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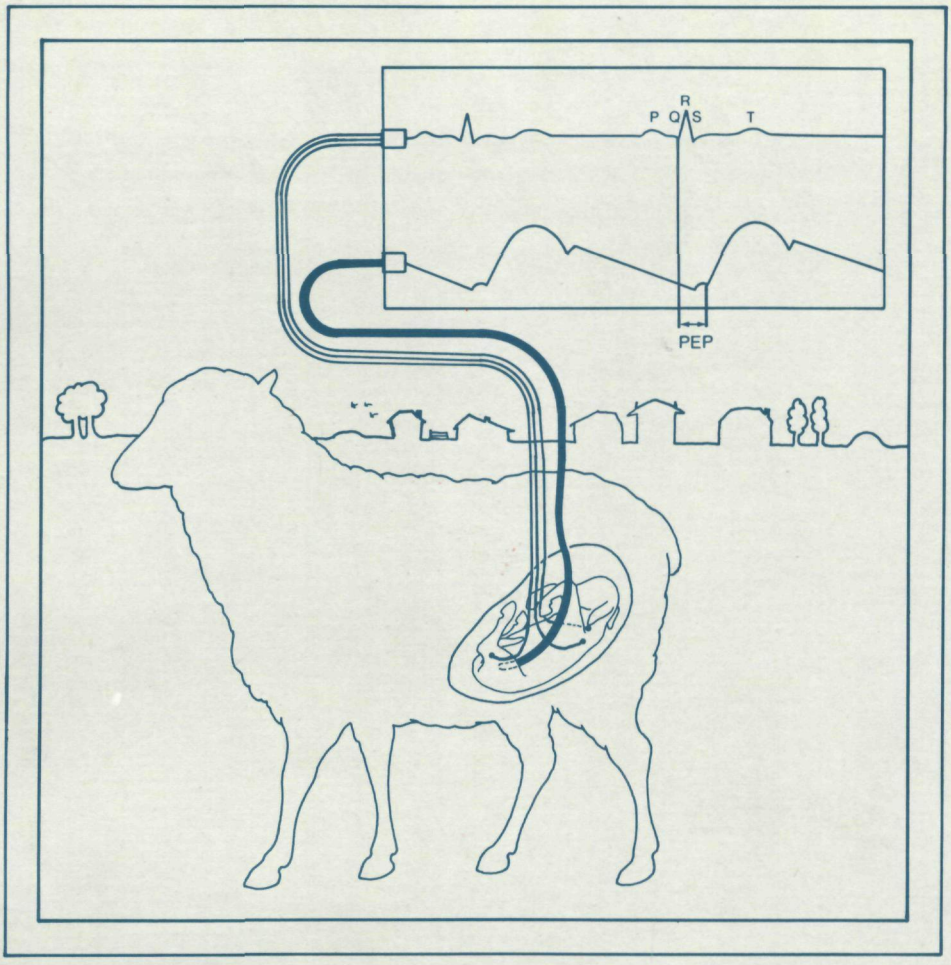

the cardiac pre-ejection period during prenatal life

studies in stressed and unstressed fetal lambs

hans evers

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studies in stressed and unstressed fetal lambs

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE GENEESKUNDE AAN DE KATHOLIEKE UNIVERSITEIT TE NIJMEGEN, OP GEZAG VAN DE RECTOR MAGNIFICUS PROF. DR. A. J. H. VENDRIK, VOLGENS BESLUIT VAN HET COLLEGE VAN DECANEN IN HET OPENBAAR TE VERDEDIGEN OP 8 JUNI 1978 DES NAMIDDAGS TE 4.00 UUR

door

Johannes Leonardus Henricus Evers
geboren te Roermond

1978
Krips Repro – Meppel

In dank opgedragen
aan Marion, aan mijn
vader en moeder en aan
allen die aan de tot
stand koming van dit
proefschrift hebben
meegewerkt.

Dit proefschrift kwam tot stand binnen de afdeling Obstetrie en Gynaecologie van het Sint Radboudziekenhuis, Katholieke Universiteit te Nijmegen.

Velen van hen die werkzaam zijn of waren op de afdeling Obstetrie en Gynaecologie hebben een bijdrage geleverd aan dit onderzoek. Van hen dient met name genoemd te worden Jane Crevels die assisteerde bij de operaties en de experimenten.

Prof. Dr. C.B. Martin jr. from Los Angeles, University of Southern California is mentioned for his contribution in discussing the subject of this thesis and for his suggestions concerning the language.

De medewerkers van het Centraal Dierenlaboratorium en de Proefdierenboerderij van de Katholieke Universiteit te Nijmegen wil ik bedanken voor hun hulp bij de anesthesie en de operaties en voor de perinatale begeleiding van schape-moeder en kind.

De analyse van de bloedmonsters vond plaats op het Klinisch Chemisch Laboratorium van de afdeling Obstetrie en Gynaecologie.

De tekeningen en grafieken werden gemaakt door mevrouw M.L.A. Ackermans-de Leeuw en door de heer J. Maas van de medische tekenkamer. De foto's werden vervaardigd op de afdeling medische fotografie.

De heer E. de Graaff van de medische bibliotheek was behulpzaam bij het oplossen van problemen betreffende de geraadpleegde literatuur.

De statistische bewerking vond plaats op de Mathematisch Statistische Adviesafdeling van de Katholieke Universiteit te Nijmegen.

Dick Evers is verantwoordelijk voor de cover design van dit proefschrift.

Mijn collegae assistenten in opleiding ben ik erkentelijk voor het overnemen van een gedeelte van mijn klinische taken teneinde aldus voor mij tijd vrij te maken om dit alles op schrift te stellen.

Louis Peeters voorzag het manuscript van een aantal waardevolle aantekeningen.

Staf en personeel van de 834 HKR en van de Stafstafverzorgingscompagnie Koninklijke Landmacht wordt dank gebracht voor de soepele wijze waarop telkenmale weer vele uren "vrij van werkelijke dienst" kon worden georganiseerd.

IBM Nederland stelde de schrijfmachine beschikbaar waarop de definitieve versie van dit proefschrift werd getyped.

Dit zijn de enige regels van dit proefschrift welke ik zelf type. Ik wil ze benutten om jou, Marion, te bedanken voor je bijdrage aan het tot stand komen van dit werk. Voor het typen van de vele versies van het manuscript, voor de lay-out van de definitieve tekst, voor de kritische kanttekeningen en voor je vertrouwen in het welslagen van het project.
Fenneke wil ik mijn verontschuldigingen aanbieden voor de veelvuldigheid waarmee zij in het kader van het tot stand komen van dit proefschrift bij anderen heeft moeten bivakkeren.
Mijn nog ongeboren dochter/zoon vraag ik op voorhand excuus voor het feit dat zij/hij de eerste acht maanden van haar/zijn prenatale bestaan heeft moeten doorbrengen op nauwelijks 30 centimeter van een ratelende schrijfmachine.

Nijmegen, 12 april 1978

Hans Evers

GLOSSARY

AA	occlusion of both umbilical arteries
A*	occlusion of both umbilical arteries after atropine administration
AF	occlusion of both umbilical arteries after phentolamine administration
AP	occlusion of both umbilical arteries after propranolol administration
APGAR	scoring system for the evaluation of the newborn infant
AV-block	atrioventricular block
BE	base excess (in mmol/L)
BP	blood pressure (in mmHg)
b.p.m.	beats per minute
B.W.	fetal body weight (in kg)
DAP	diastolic aortic pressure; afterload
DCG	Doppler cardiogram
EDVP	end-diastolic ventricular pressure; preload
EMD	electromechanical delay
ewe 12-75	sheep number; first two digits indicating number of ewe, digits behind dash indicating year of experiment (1975,1976,1977 or 1978)
FHR	fetal heart rate (in b.p.m.)
FECG	fetal electrocardiogram
FPhCG	fetal phonocardiogram
G.A.	gestational age (in days)
G.W.	gestational age (in weeks)
Hb	hemoglobine
heart period	R-R interval
hr	hour (h)
I*	occlusion of maternal common internal iliac artery; after atropine administration
IF	occlusion of maternal common internal iliac artery; after phentolamine administration
II	occlusion of maternal common internal iliac artery
IP	occlusion of maternal common internal iliac artery; after propranolol administration
IVC	isovolumetric contraction time
kPa	kiloPascal (1 kPa = 1 N/m^2 = 7.5 mmHg)
m	mean
mmHg	millimeters of mercury
msec	milliseconds (ms)
N.S.	not significant ($p > 0.05$)
p	tail probability
PCO_2	partial pressure of carbon dioxide (in kPa)
PEP^2	pre-ejection period; EMD + IVC. In the present report the PEP is defined as the interval between a fixed trigger point in the QRS-complex and the onset of the upstroke in the aortic blood pressure
pH	degree of acidity; negative logaritm of hydrogen ion concentration in equivalents per liter
PO_2	partial pressure of oxygen (in kPa)
QS_1^2	interval between Q-wave in the ECG and the first heart sound
QS_2	electromechanical systole; interval between the Q-wave in the ECG and the second heart sound (PEP + VET)

$\underline{r}$	correlation coefficient
$\bar{r}_s$	average value of Spearman's rank correlation coefficient
R-R interval	heart period; interval between two successive R-waves in ECG (in msec)
S_1	first heart sound
S_2	second heart sound
S_1S_2	interval between first and second heart sound
SA-node	sinoatrial node
S.D.	standard deviation
S.E.M.	standard error of the mean
SH 1234	code of experiment: SH = sheep; 12 = sheep number; 34 = experimental number
SO_2	oxygen saturation
T*	occlusion of total umbilical cord after atropine administration
TF	occlusion of total umbilical cord after phentolamine administration
TP	occlusion of total umbilical cord after propranolol administration
TT	occlusion of total umbilical cord
U	units
V*	occlusion of both umbilical veins after atropine administration
VET	ventricular ejection time
VF	occlusion of both umbilical veins after phentolamine administration
VP	occlusion of both umbilical veins after propranolol administration
VV	occlusion of both umbilical veins

C O N T E N T S page

"Knowing as we do that intrauterine anoxia actually kills such a large number of infants, would it not be logical to believe that sometimes the degree of anoxia may not be quite sufficient to kill the infant but enough to inflict irreparable injury to the cerebrum?"

Nicholson J. Eastman
"Mount Everest in utero" - 1954

Ever since the publication in 1863 of Little's "On the influence of abnormal parturitions, difficult labors, premature births and asphyxia neonatorum on the physical and mental condition of the child, especially in relation to deformities", there has been a widespread discussion concerning the possible influence that intrauterine hypoxia, whether ante- or intrapartum, might exert upon the postnatal development of a child. There has been a growing awareness of the fact that, apart from the number of children succumbing of intrauterine asphyxia, there must be a probably even more extensive group of children whose brains never had the opportunity to develop fully according to their capacities, due to irreversible damage done by an intrauterine hypoxic insult to the centers most sensitive to oxygen lack, i.e. those governing speech, muscle coordination and reason.
The early detection of possible causes of fetal distress and the preservation of an optimal starting point for the child's future development have always been the principal objectives of those whom women have trusted the care of their pregnancies to.

Takemura (1973) compiled the findings from fetal research into a working hypothesis for a pathophysiological classification of perinatal depressions. He discerned three different types of fetal distress:

- Acute fetal distress, consisting of acute, primary respiratory acidosis of the fetus, due to umbilical blockade of fetal oxygenation, resulting in a sudden decrease of PO_2 and a rapid accumulation of carbon dioxide.
- Subacute fetal distress, when the fetal oxygenation is impeded by recurrent uteroplacental insufficiency, most often caused by a too frequent uterine contraction pattern, by hypertonia or by a decrease in maternal uterine blood supply.
- Chronic fetal distress, consisting of chronic, primary metabolic acidosis of the fetus, due to longstanding disorders in the mother. Cardiopulmonary complications, such as cyanotic heart disease or heavy smoking are the cause of maldevelopment of the fetus, who even might not have sufficient energy reserves to stand the stress of labor. Also the complications of toxemia of pregnancy, maternal anemia, diabetes or Rhesus incompatibility are known as a cause of functional maternal blockade and/or organic placental blockade of fetal oxygenation and nourishment.

A spectrum of diagnostic procedures has been developed with a view toward the early detection of fetal deterioration during pregnancy and during labor.
Apart from the physical examination, auscultation, amnioscopy and ultrasound-procedures, laboratory tests of fetal well-being have become available nowadays: Among these, the determination of maternal urinary estriol and pregnandiol levels, human placental lactogen, alpha-fetoprotein and examination of the amniotic fluid obtained by needle amniocentesis, e.g. for the concentration of bilirubin (OD_{450}).
The two most important methods applied in present perinatal care for the detection of complications during labor are fetal scalp blood sampling, introduced by Saling (1962) and, possibly the greatest advance in recent obstetrics, the simultaneous monitoring of the fetal heart rate and uterine activity, introduced by Hon et al. (1960), Hammacher (1962) and Caldeyro-Barcia et al. (1963).

Possible new directions in perinatal intensive care that are currently under investigation are the detection of fetal respiratory and total body movements, the elaboration of the registration of beat-to-beat variability in the fetal heart rate, the determination of fetal systolic time intervals and the continuous measurement of PO_2 and pH. The determination of systolic time intervals in the adult was introduced by Garrod in 1874. The first to indicate the value of these parameters as an indirect measurement of the cardiac function was Wiggers in 1921.
In the present report the results are published of an investigation into the behavior of the pre-ejection period (PEP) of the cardiac cycle in the fetal lamb in utero, during umbilical cord occlusion and during simulated (sub)acute uteroplacental insufficiency. The PEP has been found to be a reliable indicator of cardiac performance (Lewis, 1974). It was however not the reliability of the PEP as an indicator of fetal cardiac performance that was evaluated in the present study, but rather the nature of the changes induced in the duration of this phase of the fetal cardiac cycle by both earlier mentioned conditions of fetal distress, umbilical cord occlusion and (sub)acute uteroplacental insufficiency. This investigation originated in the assumption that, by studying the changes induced by umbilical cord occlusion and (sub)acute uteroplacental insufficiency, an idea could be obtained concerning the possible role of the PEP as an index of acute fetal distress.

Organ et al. (1973b) have found, in the acute fetal lamb preparation, a prolongation of the PEP during the tightening of a loop of umbilical tape around the exposed umbilical cord, whereas it shortened when the 100 per cent oxygen supply to the ewe was replaced by 100 per cent nitrogen.
The questionable reliability of results obtained in the acute experiment (Shelley, 1973; Rudolph and Heymann, 1974; Vatner, 1975; de Haan et al., 1975b, 1976b) with the fetus exteriorized (Heymann and Rudolph, 1967), and the scantiness of figures

from PEP-determinations in the fetus were the stimuli to study this parameter in the chronic fetal lamb preparation.

Although the unstressed chronic laboratory preparation may be unlike the human fetus, it is only the carefully prepared chronic fetal preparation that allows a precise study of the various fetal cardiovascular responses to specific stressful conditions.

CHAPTER 1

HISTORICAL REVIEW

In the first section of this chapter the developments in cardiovascular research will be reviewed that initiated the investigation of the individual intervals of the cardiac cycle. Subsequently the introduction of these intervals in fetal research will be discussed. The possible significance of changes in fetal systolic time intervals, especially the PEP, in relation to some presumed sources of fetal distress will be discussed with the aid of the results of Murata's group in Los Angeles and Organ's group in Toronto.
Finally the results will be reviewed of other fetal research centers.

1.1 Early developments

1.1.1 Adult cardiovascular research

The most important contribution to the study of individual intervals in the action of the heart can undoubtedly be attributed to Harvey, who described the systole in 1628 in his "Excercitatio anatomica de Motu Cordis et Sanguinis in animalibus" as the phase in the cycle of the heart during which the blood is pumped out of the heart into the circulation of the body. Harvey was the first to take the pumping action of the heart into consideration, thus laying the basis for cardiovascular physiology as a study in the nature of human life.

After the Dane Stensen had revealed the muscular structure of the heart and van Leeuwenhoek had shone his light on what we know today as the "pulse", more attention was paid to the development of experimental methods through which the cardiovascular system could be observed and explored.

Hales (1733) is often considered as the founder of research into hemodynamics, because of the results of his blood pressure experiments in horses. The introduction of percussion by the Austrian Auenbrugger in 1761 and of the stethoscope and thus of auscultation by the Frenchman Laennec in 1819 made the human heart and circulatory system finally accessible to "physiologic" investigations.
After von Kölliker and Müller had shown in 1856 that a frog's heart produces electrical currents, and Waller had demonstrated in 1887 how the heart potentials could be registered in in a non-invasive manner by the use of electrodes applied to the surface of the skin, it was not until 1903 that Einthoven laid the basis for modern electrocardiography by introducing his modification of the string-galvanometer.

In spite of the steadily increasing number of attempts all over Europe to fathom the functions of the human body, little notice was taken of an investigation into what would later be termed the "systolic time intervals":
On April 23, 1874 Sir Alfred Baring Garrod presented a paper to a meeting of the Royal Society of London in the name of his 28 year old, then already unrecoverably ill son, Alfred Henry, entitled "On some Points connected with the Circulation of the Blood, arrived at from the study of the Sphygmograph trace". Through this presentation notice was finally taken of the individual phases which can be differentiated within one cardiac systole.
With the help of the sphygmomanometer, Alfred Henry Garrod distinguished between a "Cardiosystole", the interval between the beginning of the systole and the closing of the aortic valve, and a "Sphygmosystole", between the opening and closing of the aortic valve. He poses:"(...) by subtracting the shorter sphygmosystole from the longer cardiosystole a remainder is obtained which can be nothing else than the expression of the time, occupied by the ventricle at the commencement of its systole in elevating its internal pressure to that of the blood in the aorta, which must occur before the aortic valve can open up. This interval is named the syspasis."

It was not until 1921 that attention was redirected to the systolic time intervals in Wiggers' "Studies on the consecutive phases of the cardiac cycle".
He introduced the term "isometric contraction" of the ventricles. In acute animal experiments and in adult human subjects he systematically studied the influence of the heart frequency, venous return, and arterial blood pressure upon the duration of the individual phases of the cardiac cycle.
Wiggers (1921) observed that the isometric contraction phase was shortened by an increase in the venous return, whereas there was no change in the duration of this phase in consequence of vagotomy or stimulation of the distal vagus nerve end.

The administration of epinephrine caused a shortening of the isometric contraction phase. He could not show a consistent change in this phase when arterial blood pressure was changed, either by stimulation of the central vagus nerve, or by compression of the aorta following vagotomy.

In 1923 Katz and Feil, studying patients with atrial fibrillation, evaluated Wiggers' results and examined the phases which he had differentiated, the isometric contraction phase and the ventricular ejection phase, subdividing again the latter into a phase with "maximum ejection" and a phase with "minimum ejection". They chose this group of patients for their investigation because with atrial fibrillation a large difference in venous pressure can be seen with a wide range of succeeding cardiac cycle lengths. Also, in this group it is only the venous return which determines the strength of ventricular contraction and not the (synergistic) atrial contractions.
Katz and Feil (1923) concluded that the relative duration of the individual phases of the systole was mainly determined by:

a) "The initial tension and diastolic volume of the ventricle".
b) "The arterial resistance".
c) "The condition of the heart muscle".

Thus ended the second period in the study of systolic time intervals.

The third and last episode began in 1966 when the developments in cardiology were progressing so well that diverse parameters had become available for the evaluation of the function of the myocardium. Harris, Weissler and co-workers in Columbus, Ohio, reported in several articles on an investigation into the relationship between individual systolic time intervals and other indices of the myocardial function, both in normal subjects and in patients with cardiovascular defects (Harris et al., 1966; Harris et al., 1967a;
Weissler et al., 1968; Weissler et al., 1969; Garrard et al.,

1970; Talley et al., 1971; Leighton et al., 1971; Pigott et al., 1971; Sherman et al., 1972; Lewis, 1974; Lewis et al., 1976). They showed the close connection between ventricular ejection time (VET), heart rate and stroke volume, both in the normal group and in the group with dysfunction of the myocardium. It is this group of investigators that (in 1966) renewed interest in the meaning of Garrod's syspasis, c.q. Wiggers' isometric contraction phase. This phase, together with the electromechanical delay (EMD) - between the Q-wave in the ECG and the onset of intraventricular pressure rise - they called the pre-ejection period, or PEP.

Greenfield et al. (1968) investigated the relationship between beat-to-beat variations in stroke volume, measured with the help of a catheter flow meter in the proximal aorta, and changes in the PEP and the VET in patients with atrial fibrillation(cf.Katz et al.,1923)and with atrio-ventricular dissociation. In their studies, where the stroke volume varied spontaneously while at the same time changes in intrinsic contractility of the heart muscle and in afterload were minimal, they showed that the PEP was inversely proportional to the stroke volume over the complete range of observations (PEP 50-200 msec).
Comprehensive investigations of the systolic time intervals and their value as indices for the contractility of the myocardium were made possible by the development of more exact diagnostic methods such as the ultrasound cardiography, electromagnetic flow measurements, catheter tip micro-manometers, heart catheterization and X-ray ventriculography. Application of these techniques to adult human subjects led to the following conclusions regarding the PEP:

- An increase in heart rate caused by the application of pharmacologic adrenergic stimulation is coupled with a shortening of the PEP, a result of the inotropic properties which these drugs possess in addition to their chronotropic ones (Raab et al., 1958; Harris et al., 1967a).

- A similar shortening of the PEP is not observed when an increase in the heart rate is achieved by blocking the parasympathetic nervous system, either by severing the vagus nerve or by a pharmacological block (atropine)(Raab et al., 1958).
- There is also no shortening of the PEP observed if the heart rate is increased by means of electrical cardiac stimulation (atrial pacing)(Leighton et al., 1969).
- A prolongation of the PEP is seen in association with parasympatnetic stimulation of the heart (Harris et al., 1967b;) This finding is in contrast with what was observed by Wiggers in 1921, that central vagus nerve stimulation had no negative inotropic effect (Wiggers, 1921).
- An increase in the stroke volume caused by an increase in ventricular filling (preload) is accompanied by a shortening in the duration of the PEP (Greenfield et al., 1968; Harley et al., 1969)
- An increase in the afterload of the heart (aortic diastolic pressure) causes a lengthening of the PEP; a decrease in the afterload causes a shortening (Harris et al., 1966; Harris et al., 1967a).
- A chronic increase in the arterial blood pressure chronically prolongs the PEP (Weissler et al., 1968).

Once a more critical determination of the relation between cardiac performance and its non-invasively obtained parameters was made possible by means of the new quantitative techniques for evaluating the working capacity of the heart muscle (Reeves et al., 1960; Mason et al., 1969; Metzger et al., 1970; Talley et al., 1971; Vonk et al., 1974; Lewis et al., 1974; Willems et al., 1975; v.d. Werf et al., 1975; Stefadouros et al., 1975; Hirschfeld et al., 1975; Abel, 1976), the most logical following step was the determination of the value of the systolic time intervals in reference to diagnosing patients with a defective cardiac function.

Weissler et al. saw a lengthening of the PEP and a shortening of the VET in untreated patients with diminished left ventricular performance as, for instance, in myocardial defects due to coronary arterial sclerosis, hypertension and primary diseases of the myocardium (Weissler et al., 1968).
The total electro-mechanical systole (QS_2) stayed within the normal ranges (Weissler et al., 1968; Weissler et al., 1969). When the cardiac output of these patients was measured, significant correlations were demonstrated between the stroke volume and cardiac output on the one hand and the PEP and VET on the other. Patients whose hearts were only slightly affected (class I or II in the New York Heart Association classifications) and in whom the cardiac output and stroke volume were only slightly decreased had only a slight deviation in the duration of the PEP and VET. Patients with a more serious disorder in myocardial function (New York Heart Association classifications III and IV) demonstrated greater abnormalities in the PEP and VET.

The PEP/VET ratio was proposed by Weissler et al. (1969) as a measurement of myocardial contractility since in the aforementioned group of patients they found that a decline in the performance of the heart was coupled with a lengthening of the PEP, while at the same time the VET was shortened and the QS_2 stayed stable.
A similar proposal had been offered earlier by Margolis et al. (1964) in reference to the ratio of VET to IVC (isovolumetric contraction time).
The investigation into the usefulness of systolic time intervals in clinical diagnosis was enlarged and systolic time intervals were determined in patients with chronic cardiac decompensation (Weissler et al., 1968), valve defects and valve protheses, acute pericarditis, aortic insufficiency, ischemic cardiac defects, cardiomyopathy (Garrard et al., 1970), acute myocardial infarction (Lewis et al., 1972), hypertension (Weissler et al., 1968), as well as coronary blood vessel

defects (Lewis et al., 1976), in adults and children (Golde et al., 1970; Hirschfeld et al., 1975).
At the same time, the systolic time intervals were measured in exercise tests using ergometers (Pigott et al., 1971; Clerens et al., 1973; v.d. Hoeven et al., 1973).
Adolph et al. (1969) and Greenfield et al. (1968) studied the systolic time intervals in patients with conduction disorders and Sherman et al. (1972) in patients with arrhythmias.

1.1.2 Fetal cardiovascular research

The positive results of the investigations into the non-invasive determination of systolic time intervals within the framework of adult cardiology renewed the interest in perinatal research units in a diagnostic method which had been known already for years in the obstetrical departments, the simultaneous registration of the ECG and phonocardiogram of the fetus.
Fetal heart sounds were authentically heard for the first time in 1822 by Kergaradec. After Cremer (1906) had introduced FECG-recordings and Hofbauer and Weiss (1908) obtained the first phonocardiogram of fetal heart sounds, in 1941 the two parameters, FECG and FPhCG, were studied together for the first time, independently by Pütz and Ullrich in Germany, and Dressler and Moskowitz in the United States. The objective of both investigations was to show a possible way to facilitate the detection of fetal QRS-complexes, by confining their occurrence area to that part of the ECG-tracing immediately preceding the first phono-signal. So, in fact, Pütz and Ullrich show in their "besondere Methode, um den geometrischen Ort, an dem auch kleinste kindliche Aktionszacken zu erwarten sind, einwandfrei zu bestimmen", the first registration of fetal electromechanical cardiac time intervals in obstetrics. The first, however,to see a clinical significance in these intervals between electro- and phono-cardiographic registration of the fetal heart action, were Kelly in 1965 and

Persianinov et al. in 1966. A distinction was made between the "asynchronous contraction phase" (QS_1, between the Q-wave of the FECG and the first heart sound, S_1), the interval between the first and the second heart sound (S_1S_2), the QS_2 or general systole and the ventricular diastole (S_2Q), defined as the interval between the second heart sound and theQ-wave of the following fetal QRS-complex.

Especially important was the finding that the asynchronous contraction phase stayed constant during both the first and second stage of labor, including basal cardiac rhythm and bradycardia during expulsion, whereas the duration of the mechanical systole increased during a deceleration and the duration of the QRS-complex does not change (Persianinov et al., 1966).

Persianinov et al. (1966) stated that the vagus nerve influenced the fetal heart frequency but did not influence the contractility of the fetal myocardium. They erroneously thought that it was exclusively a change in the regulation via the vagus nerve during delivery that was responsible for the fact that the systolic time intervals they had recorded showed little consistent variations during expulsion.

A better explanation for this finding is probably found in the non-optimal capacity, both electrically and mechanically, of the technical registration possibilities which they had access to. Furthermore, the stochastic character of the first heart sound is not conducive to an exact determination of its beginning and end.

Although Persianinov et al. (1966) did not apply the same systolic time intervals which were being used at that time in cardiology, their observations that the asynchronous contraction phase is the same during basal fetal heart activity (average of 39 msec with a range of 30-50 msec) is in agreement with the findings of investigations into systolic time intervals in adults done elsewhere (Harris et al., 1967a).

Harris et al.(1967a) showed that ff a change in the PEP appeared under the influence of various stimuli, in the majority of

cases this reflected not a change in the duration of the phase of electromechanical delay (in agreement with Persianinov's asynchronous contraction phase), but rather of the isovolumetric contraction phase.

In 1968 Peeters refers to the possible advantages that registration of real systolic time intervals can offer in perinatal care. Because he did not have adequate techniques at his disposal, Peeters limited himself to the method which Persianinov and others had applied: a combination of the abdominally conducted FECG and the fetal phono-signal.

He discovered that the interval QS_2 between the Q-wave in the FECG and the second heart sound is shortened noticeably in a fetus with hydrops as a result of erythroblastosis fetalis.

In 1972 Goodlin et al. attempted a registration of the PEP of a human fetus in utero, using three signals: the FECG, the phono-cardiogram and the peripheral pulse wave form, as recorded from the fetal scalp.

These investigators calculated the electromechanical systole as the interval between the Q-wave in the FECG and the second (phono) heart sound, and the VET as the interval between the start of pressure rise in the fetal scalp vessel and the moment of the incisural notch in this pulse tracing.

By subtracting this VET from the QS_2 they got an interval that, theoretically, should be more or less equivalent to the PEP as determined in cardiology. The PEP calculated in this way varied between 41 and 60 msec. The variation was attributed to measurement inconsistencies. This way of calculating the PEP encounters a difficulty in so far that, as v.d. Werf and colleagues (1975) demonstrated, the pulse wave form is changing while passing through the arterial tree.

The VET measured by the peripheral pulse procedure shortens less with rising heart rates than does the original one as it is recorded directly from the heart. This may quite well be an explanation for the fact that all the investigators applying this peripheral pulse registration method (Goodlin et al., 1972; Weissler et al., 1969; Organ et al., 1973b) find a

close inverse relationship of the PEP with heart rate, while others, using the Doppler signal do not (Murata and Martin, 1974a).

Insurmountable technical problems were the reason for Goodlin et al. (1972) to limit their research to a study of QS_1, QS_2 and S_1S_2 which were possible to determine with the help of the FECG and phono-cardiogram only.
Goodlin et al. (1972) made the remarkable observation that the QS_1 interval was lengthened during bradycardia in a distressed fetus (1 min Apgar score 1, cord artery pH 6.92) but that the QS_1 interval did not change during a comparable degree of bradycardia in a fetus which scored Apgar 9 (1 min value).

Barcroft (1946) proposed 2 mechanisms which can cause fetal bradycardia:

1. Vagal (parasympathetic) stimulation
2. Hypoxia of the myocardium

Goodlin states that vagal reflex bradycardia is clinically much less important than "hypoxic bradycardia" and therefore sees the QS_1-determination as an important means for differentiation between the two.

Summarizing, the possible significance of determining the PEP of the fetal cardiac cycle was recognised already in 1972. The supposition that the PEP could play a role as an indicator of a change in fetal cardiovascular conditions caused by fetal distress was based upon the finding in adult cardiovascular research that the duration of the PEP was determined principally by two factors:

1. the myocardial contractility, reflected in the rate of intraventricular pressure rise (dp/dt).
2. the loading conditions of the heart, i.e.:
   -the end-diastolic ventricular pressure ("preload")
   -the diastolic aortic pressure ("afterload").

The contributions of each of these factors to the eventual duration of the PEP will be discussed in chapter 2.

Because of failing technical facilities, the actual investigation of fetal systolic time intervals was virtually limited to the results obtained by combining fetal ECG and phonocardiogram until the early seventies.

1.2 Current developments

1.2.1 Results from Murata's and Organ's investigations

The combined use of the fetal heart's electrical and phonosignals took place in anticipation of the moment that better techniques for the determination of systolic time intervals would become available. That moment seemed to have arrived already one year before when Murata, then in Osaka, published the results of an investigation attempting to record human fetal cardiac motion by means of M-mode ultrasonic cardiography (UCG) (Murata et al., 1971).
Using a 800 Hz high-pass filter on the fetal Doppler signal, he was able to detect the opening and closing of the individual valves. No differentiation was made between the aortic valve and the pulmonary valve. Because both halves of the heart function simultaneously and thus form the parts of one cardiac pump in the fetal circulation, these differentiations do not have to be made. Murata was the first who was able to record the PEP of a fetus in utero and doing so found:

$$PEP\ (m \pm S.D.) : 71 \pm 8\ msec$$

Murata's demonstration that it was possible to determine the PEP of a fetus in utero stimulated the study by Organ's group in Toronto into the behavior of this parameter in the acute sheep experiment (Organ et al., 1973a). They found that the PEP was shortened during hypoxemia, and lengthened during umbilical cord occlusion, and attributed the shortening of the fetal PEP during hypoxemia to a catecholamine release by the fetal adrenal tissue and the lengthening of the PEP during umbilical cord occlusion to changes in arterial blood pressure (see chapter 2).
In 13 term fetal lambs they found:

$$PEP\ (m \pm S.D.) : 65 \pm 8\ msec$$

In a related paper Organ et al.(1973b) describe results of an investigation of the PEP in human fetuses during labor.Using Murata's filtered Doppler ultrasound techniques (bandpass filter centered at 1000Hz) in combination with the fetal scalp lead electrocardiogram they found values which were in agreement with Murata's original ones:

$$PEP\ (m \pm S.D.) : 73 \pm 10\ msec$$

In 1974 the first results are published of monitoring the PEP together with fetal heart rate and uterine contractions in a series of unselected patients in labor (Organ et al., 1974). In a case report study the PEP was reported to alter in a way comparable to the changes that were observed by Organ and associates in the acute fetal sheep preparation: prolongation of the PEP when heart rate patterns suggested cord occlusion (variable decelerations) and abbreviation of the PEP when the FHR-tracing fastened suspicion upon a solely hypoxemic cause of fetal distress (late deceleration patterns).
Technical problems were considerable however and a consistent PEP recording difficult to attain. Organ states that technologic problems still were too big to permit routine clinical measurement of the PEP as a parameter of fetal distress, and that a practical status for general use would not be gained till aortic valve opening could be detected more consistently, either by improving the filtered Doppler technique or by developing alternative ones.
Both improving the existing technique and searching for alternative ways of detecting aortic valve opening were subject to research in the Toronto department. First a design was published for a real time fetal cardiac PEP-monitor (Cousin et al. 1974); then arterial pulse time, from the onset of the fetal QRS-complex to the arrival of the arterial pulse wave at the fetal head, was proposed as an alternative for PEP measuring during labor (Bernstein et al., 1976). A miniature compression type piezo-electric accelerometer was used to detect the arrival of the pulse wave in the fetal scalp vessels. This

technique is based upon the principle that arterial pulse wave velocity, which now is introduced as an extra variable among the PEP determinating factors, does not show a significant variation between fetuses.
It was concluded that, since arterial pulse time differs from the PEP only by a constant segment of time, the former may prove to be useful as an indicator of the PEP (Bernstein et al., 1976).

Murata who at first recorded human fetal PEP by means of filtered fetal cardiac Doppler signals (Murata et al., 1971), moved to Los Angeles and, together with Martin, started to work at an extensive study towards the behavior of the PEP during steady state antepartum and during fetal distress, both in animal experiments and in human fetuses near term and during labor.

Using the fetal scalp lead electrocardiogram and a filtered (600-2000 Hz bandpass filter) Doppler ultrasound signal, they recorded fetal systolic time intervals during labor (Murata et al., 1974a).
The several systolic time intervals were measured during 80 to 90 cardiac cycles in each of 15 normal fetuses in early labor. The PEP was found to be independent of the fetal heart rate. Of all the studied intervals the PEP appeared to be the most consistent because its standard deviation was smaller in proportion to duration than was the case with the other intervals. In addition, the PEP was the interval about which already much clinical and laboratory data in adult cardiovascular research had been gathered; so this interval appeared to be worth a further investigation as an index of fetal distress.
Simultaneous Doppler and FECG records were obtained in 15 healthy human fetuses during labor between 36 and 40 weeks of gestation. None of these fetuses showed ominous FHR-patterns, nor was any of these fetuses depressed at birth, and

all had normal courses in the newborn nursery. The PEP in this group was (Murata et al., 1974a):

$$PEP\ (m \pm S.D.) = 67 \pm 6\ msec$$

There was a linear increase in PEP with gestational age over the range of 36 to 40 weeks ($r = 0.91$).
Concimitantly simultaneous Doppler and FECG records were also studied in a group of 8 fetuses with abnormal FHR-tracings and/or an abnormal course in the newborn nursery. No serious abnormalities however were included into this group and none of the infants was clinically depressed at birth. In each of these 8 cases the PEP was above or at the upper limit of the range observed in the normal subjects according to their gestational age.
The investigators suggest that the PEP may prove to be a sensitive indicator of mild fetal hypoxemia and beginning acidosis during labor.
During antepartum measurements (Murata et al., 1974a), 70 determinations in 48 fetuses, the mean value of PEP was 62.3 msec, about 5 msec shorter than observed during labor.
30 patients delivered within one week following the PEP measurement. The PEP was greater than 70 msec in 8 fetuses. Of these, seven developed late decelerations in the FHR-pattern during labor or during a subsequent contraction stress test.
PEP was shorter than 70 msec in the remaining 22 fetuses and only one developed late FHR-decelerations after 12 hours of labor.
The PEP appears to be an early antepartum indicator of possible difficulties to be expected during labor.
In the chronic monkey preparation (Murata et al., 1974b) the PEP was found to be independent of heart rate, to increase slightly with increasing fetal age and to be positively correlated to fetal diastolic blood pressure. In addition, a strong negative relationship was found between fetal pH and

PEP, while PEP appeared to be unrelated to fetal PO_2. The degree of hypoxia however was not stated. In the chronic sheep experiment these findings were confirmed (Murata et al., 1976a), and during a study of the fetal PEP in diabetic patients a close correlation of the fetal PEP with neonatal body weight was found (Murata et al., 1976c). In a review article Murata and Martin (1977), quoting unpublished results, note a highly significant association between prolongation of the PEP before birth and subsequent evidence of fetal or neonatal distress.

The earlier reported strong negative correlation of the PEP with arterial blood pH (Murata et al., 1974b; 1976a) was reconfirmed in these chronic monkey experiments (Murata et al. 1978a). The prolongation of the PEP with a decrease in fetal arterial blood pH was similar whether the acidemia was produced by administration of high CO_2 mixtures to the mother, by metabolic or mixed acidosis occurring during labor, or by direct infusion of dilute hydrochloric acid into the fetus. The pH ranged in these fetuses between 6.99 and 7.25. Hypoxemia alone (PO_2 17-25 mmHg) or hypoxemia associated with acidemia (PO_2 14-25 mmHg; pH 6.99-7.25) were both accompanied by a prolongation of the PEP. The authors suggest the effect of acidemia upon the duration of the PEP to be greater, since the PEP exhibited a strong linear correlation with pH, whereas no such relationship existed with PO_2.

1.2.2 Results from other fetal research centers

Goodlin (1975) found the PEP to be prolonged in severely hypoxic sheep fetuses, though in a more recent paper (Goodlin 1977), also quoting unpublished results, he reports all the

various cardiac intervals reflecting performance to be shortened during the initial phases of hypoxemia, but lengthened when asphyxia occurs.
Goodlin suggests that the initial shortening of the PEP is due to an excess catecholamine release, while a decrease in myocardial contractility due to the prolonged asphyxia is held responsible for the subsequent lengthening. Unfortunately Goodlin does not give any further details about the experiments he refers to and the time sequence in which the noted PEP changes occurred.

Morgenstern et al. (1977) investigated the PEP in acute experiments in fetal sheep. They found the PEP to be lengthened during fetal head compression, while in cord occlusion experiments an initial lengthening was followed by a shortening of the PEP. Maternal hypoxemia (produced by giving low oxygen mixtures to the ewe), maternal aortic compression and maternal inferior vena cava occlusion invariably were accompanied by a shortening of the fetal PEP.

Klöck et al. (1977) measuring intrapartum PEP report a mean value of 71.7 msec $\pm$ 1.3 msec (S.D.). They found a prolongation of the PEP during mild fetal hypoxia, during fetal heart rate accelerations and during early as well as variable decelerations. A shortening of the PEP could not be demonstrated, but no serious hypoxia (viz. no late decelerations of the FHR pattern) was included in their investigation of intrapartum fetuses.

Wolfson et al. (1977), measuring the antenatal human fetal systolic time intervals with the use of the transabdominal fetal electrocardiogram and Doppler cardiogram, demonstrated the PEP to be related linearly to gestational age between 20 weeks and term.

Zacutti (1977) using the ill-defined conceptions of "hypoxic"

and "hemodynamic" decelerations, found a shortening of the PEP with the former ones, whereas a prolongation of the PEP was seen when the cause of the decelerations was presumed to be "hemodynamic".
Surprisingly, Zacutti established a positive correlation of the PEP with fetal and neonatal pH, whereas Murata and Martin found just the opposite in the chronic monkey experiment (Murata et al., 1974b; 1978a) as well as in the chronic sheep experiment (Murata et al., 1976a).

1.2.3 Results from neonatal research

Bärtling et al. (1977) determining neonatal PEP were able to record a shortening of the PEP during periods of apnea of the newborn when PO_2 fell below 20 mmHg (2.7 kPa).
An even stronger shortening of the PEP was seen accompanying situations of fetal stress, particularly crying.

Hon et al. (1975), also studying neonatal PEP changes noted a prolongation of the PEP during pure neonatal acidosis (pH 7.20) without hypoxemia (PO_2 105 mmHg).
If also the PO_2 diminished (50-60 mmHg) a shortening of the PEP was observed.

1.2.4 The PEP and fetal/neonatal/infant age

The PEP has been shown to be related to gestational age in the human fetus (Murata and Martin, 1974a; Wolfson et al., 1977; Murata et al., 1978b), fetal monkey (Murata et al., 1978a) and fetal sheep (Murata et al., 1976a). Also in infants and children (Harris et al., 1964; Hirschfeld et al., 1975) the PEP has been reported to lengthen with increasing age.
Golde et al. (1970) demonstrated that this prolongation of the PEP in children resulted from an increase in the duration of both the electromechanical delay and the isovolumetric

contraction phase.

The nearly identical rates of increase in the intervals Q-mitral closure (Q-Mc) and Q-aortic opening (Q-Ao) and in the duration of the QRS complex with gestational age in fetal monkeys, reported by Murata et al. (1978a) suggest that the prolongation of the time required for depolarization of the heart is responsible for the lengthening in both Q-Mc and Q-Ao intervals. They suggest the increase in QRS duration to be due to increasing myocardial volume (Murata et al., 1978a).

The results of PEP determinations from the various fetal research centers mentioned before are summarized in table 1.1. It should be remembered however that few authors have specified the range of gestational ages of the subjects in their population. Murata et al. arrived at the following regression equation of the PEP with gestational age (G.A.; in days) in fetal monkeys (Murata et al., 1978a):

$$PEP = 0.19\ G.A. + 17\ (msec)$$

And in normal human antepartum fetuses between 33 and 43 wks. (G.W. = gestational age in weeks) (Murata et al., 1978b):

$$PEP = 1.52\ G.W. + 4.08\ (msec)$$

Wolfson et al. (1977) calculated in normal human antepartum fetuses (20-40 weeks; G.W. = gestational age in weeks):

$$PEP = 0.85\ G.W. + 23.99\ (msec)$$

reference	human / animal	PEP (msec)	remarks
Murata et al., 1971	human	71	labor
Organ et al., 1973a	human	73	labor
Organ et al., 1973b	lamb (acute)	65	antepartum (135-147 days)
Goodlin et al., 1974	human	64	labor
Murata et al., 1974a	human	70	labor (38-40 weeks)
Klöck et al., 1977	human	72	labor
Wolfson et al., 1977	human	58	antepartum (R)
Murata et al., 1978a	monkey(chronic)	48	antepartum (R)
Murata et al., 1978b	human	65	antepartum (R)

Table 1.1: Results of PEP-determinations at the end of pregnancy, from various fetal research centers. Days and weeks refer to gestational age. Acute = acute sheep preparation, fetus exteriorized. Chronic = chronically instrumented fetal monkey preparation. R = calculated from regression equation, shown on preceding page for the end of pregnancy in man (40 wks) and monkey (165 days).

Although a considerable amount of information concerning the human PEP, antepartum as well as during labor, has been gathered, results from animal experiments are still limited to a few reports.

Meanwhile already some (premature) attempts have been made to design an automated PEP-recording system. Besides the already mentioned machine from the Toronto group (Cousin et al., 1974), also Goodlin et al. (1974) constructed a fetal cardiac interval recorder, as did Murata and associates (Hon et al., 1974). The clinical suitability of these machines apparently has not been proven sufficient to such an extent that reports dealing with a comprehensive clinical investigation of the fetal PEP have been published yet.

CHAPTER 2

PHYSIOLOGICAL BASIS FOR PRE-EJECTION PERIOD MEASUREMENTS

2.1 Electrical and mechanical events of the cardiac cycle

The heart is primarily a muscle which functions as a hydraulic pump. The filling phase and the pumping phase of this pump are represented in the intact animal by diastole and systole, respectively. The effective cardiac work performed during the contraction of the myocardial muscle mass produces the forward movement of the blood against the arterial resistance. Every single heart beat normally is initiated in the sinoatrial node (SA node) pacemaker cells. From the SA node the excitation proceeds via the atrioventricular node, the Purkinje fibers of the bundle of His and the bundle branches to the subendocardium of both ventricles. Excitation is then conducted from endocardium to the ventricular epicardium. The initial sinoatrial node depolarization becomes a confluent front which, in the human, starts to spread over the ventricular wall after about 30 msec. In response to this stimulus, synchronized mechanical activity of the cardiac muscle cells (contraction) results in the ejection of the ventricular content into the outflow tract of main blood vessels and the propulsion of the blood in these vessels and the remaining parts of the vascular system.

Prior to the ejection of the blood volume contained by the ventricles, two separate phases of the cardiac cycle can be discerned: - The electromechanical delay (EMD)

- The isovolumetric contraction (IVC)

The phase of electromechanical delay comprises the spreading of the depolarization front through the myocardial wall and the synchronization of individual muscle cell activity to a coordinated ventricular contraction. The phase of isovolumetric contraction is initiated by the onset of ventricular contraction at approximately the time of the peak of the R-wave

in the electrocardiogram. The pressure starts to rise, and at the moment it exceeds the atrial pressure the atrioventricular valves close.

The ventricles then proceed to contract on their (incompressible) volume of blood. The volume does not change and intraventricular pressure rises. At the moment that the aortic (and pulmonary artery) pressure is exceeded, the semilunar valves open and the isovolumetric contraction phase ends.

The electromechanical delay and the isovolumetric contraction together form the pre-ejection period (PEP). The PEP is thus initiated by the start of ventricular electrical depolarization and ends when the ventricular pressure surpasses the diastolic arterial pressure and the semilunar valves are opened.

2.2 dp/dt and the performance of the heart

The ability of the myocardium to alter its rate of contraction and, as a consequence, the rate of intraventricular pressure development (dp/dt), is one of its most important properties in respect to the adaptation to changing cardiovascular demands.

Starling et al. (1927) and Anrep (1912) stressed the importance of the heart's ability to change its rate of contraction in response to increases in end-diastolic ventricular pressure (preload) and diastolic aortic pressure (afterload), respectively. It has been demonstrated (Mason, 1969; Martin et al., 1971; Lewis et al., 1974) that the rate at which intraventricular pressure rises (dp/dt) during the isovolumetric contraction phase of the heart muscle, the main component part of the PEP, provides a valid and sensitive measure for the study of myocardial contractility, i.e. the ability of the heart to perform.

2.3 Factors influencing the duration of the PEP

The maximal rate of rise of ventricular pressure (peak dp/dt) is inversely related to the isovolumetric contraction time as shown by Metzger et al.(1970) in the intact dog, even when the heart's loading conditions were not controlled. The isovolumetric contraction time was shortened by the administration of isoproterenol and lengthened by methoxamine and by vagal stimulation. It would appear most appropriate to use the interval between the first heart sound and the beginning of ventricular ejection, i.e. the isovolumetric contraction time, as an index of myocardial condition. The exact onset of the first heart sound however is difficult to determine (Weissler,1977) and, moreover, it does not coincide exactly with the start of ventricular muscle contraction (Luisada et al.,1972). For this reason the entire pre-ejection period was chosen as an index of myocardial contractility. Metzger et al.(1970) and Martin et al.(1971) demonstrated an excellent linear correlation between the internally measured isovolumetric contraction time and the non-invasively determined PEP, both in steady state conditions and during a series of acute interventions, in both dogs and humans. In the acute dog experiment Talley et al.(1971) confirmed the significant correlation between the PEP and some more completely evaluated internal indices of myocardial contractility, provided the heart's loading conditions were kept constant. Martin et al. (1971) could show no significant change of the electromechanical delay during interventions associated with either a prolongation or a shortening of the PEP in adult human subjects. The major determinants of the duration of the PEP are (Lewis et al.,1974):

1. *Myocardial contractility (dp/dt)*
2. *End-diastolic ventricular pressure ("preload")*
3. *Diastolic aortic pressure ("afterload")*

Decrease in myocardial contractility (fig. 2.1) is reflected in a deficient rate of myocardial force development. The time required for the intraventricular pressure to reach the level of aortic diastolic pressure becomes increased and the PEP prolongs (Weissler et al., 1968). Vonk et al.(1974)

report a prolongation of the PEP during exercise in patients with coronary artery disease.

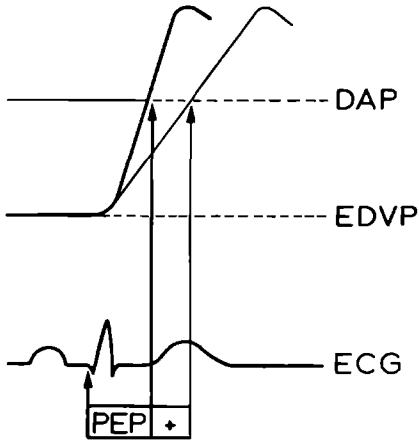


Figure 2.1: Schematic representation of the effect of a decrease in myocardial contractility upon the duration of the PEP. DAP = diastolic aortic pressure, EDVP = end-diastolic ventricular pressure.

On the other hand, as shown by Raab et al. (1958), epinephrine and nor-epinephrine shorten the pre-ejection period, reflecting the augmentation of the velocity of ventricular contraction by these inotropic agents (Wallace et al., 1963).
A similar shortening of the PEP occurs when digitalis glycosides act upon a failing myocardium (Harris et al., 1967a).
Decrease of end-diastolic ventricular pressure will not only diminish the myocardial contractile force in conformity with the Frank-Starling mechanism (fig. 2.1) but will also enlarge the pressure difference between EDVP and DAP that has to be conquered to open the semilunar valves (fig. 2.2).
Brinkman et al. (1972) in the acute fetal lamb preparation and Kirkpatrick et al. (1976) in the chronically instrumented fetal lamb demonstrated the Frank-Starling mechanism to be operative in the fetal lamb at term.

They showed resting myocardial fiber length to be of fundamental importance in fetal cardiovascular homeostasis, keeping the cardiac output unchanged over a wide range of spontaneous heart rates (114-180 b.p.m.).

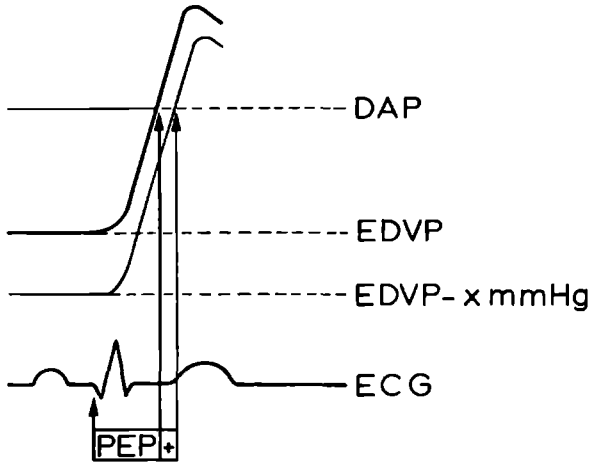


Figure 2.2: Schematic representation of the effect of a decrease in end-diastolic ventricular pressure (preload) upon the duration of the PEP. Abbreviations as used in fig. 2.1.

The effect of an increase in diastolic aortic pressure (DAP), or afterload (fig. 2.3), will be a prolongation of the PEP, since also in this situation a larger pressure step has to be overcome.

Harris et al. (1967a) demonstrated in adult human subjects that the PEP was lengthened by peripheral vasoconstriction, either effected adrenergically by nor-epinephrine, or non-adrenergically by angiotensin-II, a peripherally acting vasoconstrictor.

Nor-epinephrine in higher dosages however was found (Harris et al., 1967a) to shorten the PEP, an effect which could be prevented by the administration of a beta-adrenergic blocking agent (propranolol).

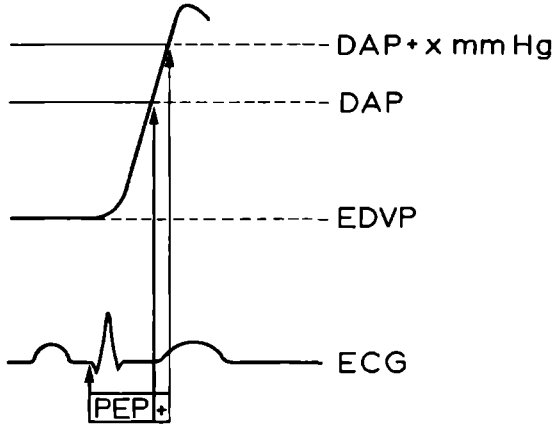


Figure 2.3: Schematic representation of the effect of an increase in diastolic aortic pressure (afterload) upon the duration of the PEP. Abbreviations as used in fig. 2.1.

Harris et al. 1967a conclude from these observations that the alpha-adrenergic effect of nor-epinephrine is predominant at the lower doses while its beta-adrenergic effect on the ventricle becomes increasingly prominent at the higher dosage levels.

Calculation of the PEP requires a recording of the beginning of ventricular depolarization and of the onset of ejection of the ventricular blood content into the circulation.
Whereas the determination of the onset of ventricular depolarization can suitably be performed by a registration of the Q-wave in the electrocardiogram, various methods have been developed to detect the onset of the cardiac ejection period:

1. Registration of the beginning of the aortic blood pressure rise by means of either a pressure transducer connected to a fluid filled catheter or a catheter tip micromanometer, and positioned appropriately in the aorta.
2. Registration of the aortic valve opening by means of a (filtered) Doppler Ultrasound signal or by means of a M-mode ultrasonocardiographic tracing.
3. Non-invasive detection of the upstroke of the carotid arterial waveform.
4. Apex-cardiography.
5. X-ray ventriculography.
6. Ballisto-cardiography.

Due to the surrounding fluid masses and tissues the last four methods do not lend themselves to use in fetal cardiac interval determination. Both of the first two have been employed in fetal research, in the sense that the use of the pressure recording method is limited to animal experiments, whereas the ultrasound methods can be used in human as well as in animal experiments.
Applying the second method, the PEP is defined as the interval between the Q-wave in the fetal ECG and the beginning of the second group of oscillations in the Doppler cardiogram, representing the opening of the semilunar valves.
The first method implies a definition of the PEP as the interval between the Q-wave in the fetal ECG and the onset of aortic blood pressure rise, as recorded by the pressure

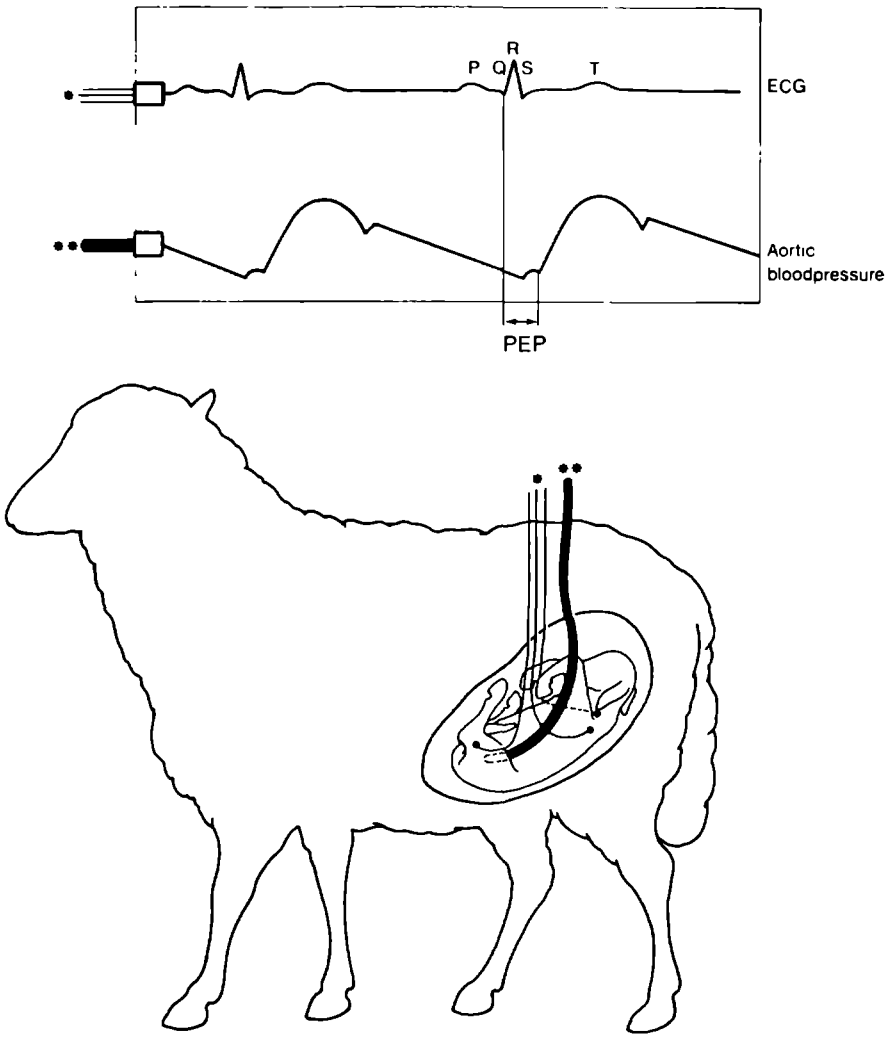


Figure 2.4: Schematic representation of the fetal pre-ejection period as the interval between the Q-wave in the fetal ECG and the onset of the upstroke in the aortic blood pressure.

transducer (fig. 2.4).

In the present report the PEP is defined as the interval between a fixed trigger point in the QRS-complex (as a substitute for the Q-wave), and the onset of the upstroke in the aortic blood pressure recording.

CHAPTER 3

MATERIALS AND METHODS

3.1 The animal

The experiments were carried out in fetal lambs from ewes of the Dutch sheep (Texel breed, a descendant from the European mouflon, ovis musimon), originating from Corsica and Sardinia. In addition, the Dutch sheep is related to some English breeds, such as Leicester and Lincoln.
Ever since Cohnstein's and Zuntz's experiments in 1884 the pregnant sheep has been the most widely used animal in fetal research. The circulation of the fetal lamb in utero is comparable to that of the human fetus. The lungs are not yet expanded and form a high vascular resistance in the fetal circulation. The three main shunts that provide the supply of oxygenated blood to the vital organs are also present in the sheep fetus:

- foramen ovale
- ductus venosus (Arantii)
- ductus arteriosus (Botalli)

The sheep species differs from man in having two umbilical veins rather than one. It possesses a cotyledonary placenta and has a relatively smaller brain. Moreover, the placental barrier in the sheep is histologically of the epitheliochorial type, in contrast to the human haemochorial placenta. The uterus of the sheep is of the bicornis unicollis type. First pregnancies are usually singleton; but in the multiparous ewe twin pregnancies are found frequently.
The mean duration of gestation in the sheep is 147 days.

All of the pregnant ewes used in this series of experiments were obtained from the farm of the Central Animal Laboratory of the Catholic University Nijmegen. Each animal was date bred and remained at the farm of the Laboratory during most of its pregnancy.

Three days before surgery (see section 3.3) , the ewe was shaved and transported to the animal laboratory. There, three more days were allowed for conditioning to the daily routine in the new surroundings. During 24 hours preceding operation the ewes were fasted but got water ad libitum. Following operation a recovery period of 24-72 hours was allowed before the experiments were begun. A frequency of one to three experiments a day was found to be compatible with continued fetal well-being throughout the whole series of experiments, as judged by the results of intermittent blood sample studies and cardiovascular parameter determinations. The period from operation till the end of each particular series of experiments ranged from 2 to 21 days.
When the experimental period was finished, either by birth or death of the fetal lamb or by deliberate removal of the catheters and transducers from the fetus, the ewe was returned to the farm, in case of continuing pregnancy to carry it to term.

3.2 Anesthesia

3.2.1 Induction

General anesthesia was induced in the ewe with pentobarbitone, 30 mg per kg body weight, intravenously. The ewe was intubated (tube with inflatable cuff, diameter 14 mm) by means of a modified laryngoscope.

3.2.2 Preparation

The last remnants of fleece over the abdomen were shaven away and the abdominal wall was cleaned thoroughly by scrubbing with soap, ethanol 70% and an iodine solution (Betadine). The animals then were placed in a left lateral Trendelenburg position and restrained upon the operating table.

3.2.3 Continuation of anesthesia

The laryngeal tube was connected to an artificial respirator (Engström ER 300) and general anesthesia was continued with halothane in a concentration of 5% initially, in a 2:1 mixture of N_2O and O_2. A ventilation pressure of up to 11 mmHg was applied, the inspiration being 50% of the respiratory cycle and the respiration frequency 18 strokes per minute.
The tidal volume in the sheep being 10 ml/kg, a respiratory minute volume of 180 ml/kg min was reached.
Thus 6 liters of nitrous oxide and 3 liters of oxygen, respectively, were administered every minute in case of a sheep weighing 50 kg.
The halothane concentration was lowered subsequently till a level between 0.5 and 1.5% was reached, depending on the reactions of the animal. In most ewes, however, this dosage of halothane was insufficient to maintain a satisfactory degree of relaxation and anesthesia. Therefore pentobarbitone was added also during surgery (5 mg per kg body weight, intra-

venously, once every hour).

3.2.4 Recovery

The N_2O/O_2 mixture was substituted by 100% oxygen administration till the ewe started to breathe spontaneously again. Then the tube was removed and the animal placed in a special transportable cart and moved to the stable of the laboratory. Here she was allowed a 24-72 hour period for recovery from the operation, during which time acid/base balance and blood gases as well as cardiovascular parameters have been shown to normalize in case of the surgical procedure applied (de Haan et al., 1976b).

3.3 Surgical procedures

3.3.1 Fetal instrumentation

A midline abdominal incision was made and the pregnant uterine horn exposed. A 4-5 cm hysterotomy was performed and a fetal hindlimb located. This was pulled out of the uterus and the fetal skin was fixed to the uterine wall with Babcock clamps. Care was taken to prevent loss of amniotic or allantois fluid. The fetal femoral artery was exposed and incised proximally to the bifurcation of the femoral artery into the cranial femoral artery and the saphenous artery (Koch, 1970). A polyvinyl catheter (length 150 cm, inner diameter 0.8 mm, outer diameter 1.6 mm) was inserted and advanced into the aorta. Three needle electrodes were placed underneath the skin and kept in place by silk sutures. The electrodes were located on one of the hindlimbs and on the left and right sides of the thorax.

3.3.2 Umbilical cord occluding device

After the hindlimb had been replaced into the uterus the region around the emergence of the umbilical cord was manipulated into the same opening in the uterine wall and also secured with the aid of Babcock clamps. The vessels in the cord were exposed and separated by blunt dissection, arteries and veins apart. Care was taken not to injure the urachus. The cord occlusion device was positioned as mentioned in chapter 3.5.1 and fixed to the fetal abdominal skin with silk sutures. The umbilical arteries were placed in one compartment and the umbilical veins in the other.

3.3.3 Common internal iliac artery occluding device

In order to position the iliac artery occluder, the uterus was lifted out of the true pelvis and outside the abdominal cavity. The bifurcation of the aorta, which is located at

the level of the lower third of the pregnant uterus, was traced. By alternating sharp and blunt dissection, the parietal peritoneum was opened and the common part of the internal iliac artery was exposed and dissected.
If necessary, an occasional lumbar or sacral branch was ligated. The occluder was placed around the vessel and a slightly loose fit allowed in order to avoid unintentional constriction of the vessel. The flexible cuff was secured by tying with sutures and in addition stabilized by closing the parietal peritoneum over it. Then the uterus was replaced into the abdominal cavity.

3.3.4 Flow transducers

Electromagnetic flow transducers were applied to ascertain the occlusion. In the case of umbilical cord occlusion experiments, the transducer was located around one of the umbilical arteries between the device and the fetal skin. It is necessary to position the flow probe between the fetus and the site of umbilical cord occlusion to avoid loss of electrode contact with the vessel, which eventually would happen should the cuff-type flow probe be located around a (collapsing) umbilical artery between the occlusion device and the placenta. The transducer was stabilized by securing the transducer cables to the fetal abdominal wall with the aid of silk sutures. To place a flow transducer around a maternal median uterine artery, the vessel was traced and with minimal blunt dissection was separated from the underlying part of the uterine wall after the visceral peritoneum had been opened. The transducer cuff then was placed around the vessel. In order to stabilize the probe and to avoid kinking of the vessel, the transducer cables were passed through a tunnel below the round ligament, made by blunt separation of the peritoneum from the uterus over a distance of 2-3 cm.
In addition the peritoneum was closed over the flow transducer.

3.3.5 End of the operation

Membranes and uterine wall were closed in two layers and peritonized, thus preventing leakage of amniotic fluid. The abdominal wall was closed, and catheters, electrodes and flow transducer cables were led to the right flank of the ewe. They were subsequently fixed to the maternal skin with the aid of silk sutures, their endings being protected by a cotton pouch sewn to the skin on the ewe's flank.

3.3.6 Removing of experimental equipment

If necessary, either because of spontaneous labor or because of death of the lamb in utero, or because of technical problems (mostly the arterial catheter becoming blocked) the experiments were finished by removing the catheters, electrodes, flow probes and occluders.

In both types of occlusion experiments, umbilical cord occlusions and common internal iliac artery occlusions, spontaneous vaginal delivery remained possible.
If only ECG-electrodes and pressure catheters were applied these would be cut and, after cleaning, redrawn through the maternal uterine and abdominal walls together with the tubing connected to the cord occlusion device. In case of more extensive fetal instrumentation and in case of the application of vessel occluders and flow probes around maternal vessels surgical removal had to be performed, even when the lamb had been delivered spontaneously

3.4 Post operative care

3.4.1 Preventive administration of antibiotics

Since infection was the most frequent cause of preparation loss after blockage of the arterial catheter, a dosage regimen of antibiotics was instituted:

a. During surgery: Ampicillin 500 mg, into the amniotic cavity.
Sodium Penicillin 500.000 U intra-abdominally.

b. The first four days following surgery: Depomycine (procainebenzylpenicillin 150.000 U and dihydrostreptomycin sulphate 250 mg per ml) 0.13 ml per kg maternal body weight, administered to the ewe intramuscularly daily.

c. Every other day thereafter: Duplocycline (benzathine benzyl penicillin 150.000 U and procaine benzyl penicillin 150.000 U, per ml) 0.67 ml per kg maternal body weight, administered intramuscularly to the ewe every other day during the remaining days of experiments.

3.4.2 Flushing of the arterial catheter

At the end of the surgical procedures the arterial catheter, which was filled with a heparin solution (1:1000), was connected by means of an external catheter to an infusion system which allowed a continuous flushing of the catheter with the heparin solution during the total duration of the experimental period (0.01 ml/hr).

3.4.3 Stay at the animal laboratory

Following the operation the ewes were allowed 24 to 72 hours for recovery. The animals were housed in specially constructed

transportable carts during their stay in the stalls of the animal laboratory, allowing mild exercise without jeopardizing the exteriorized catheters. They were given a diet of water, hay and special fodder pellets for pregnant ruminants (Versele-Laga S.A., cubes brébis 13).
Every day they were taken to the laboratory in their carts, where the occlusion experiments were performed. When no experiments were planned on a specific day only a steady state registration was made together with a 0.2 ml fetal blood sample from the indwelling arterial catheter.

3.5 Experiments

The experiments which were performed are listed in table 3.1. At the moment of surgery the gestational age of the fetal lambs varied between 100 and 138 days. The gestational ages at the time of conclusion of the experimental period in each individual lamb ranged from 109 to 149 days, and the fetal body weight (if delivered) from 1900 to 5700 grams.

kind of occlusion	number of experiments	number of fetal lambs
umbilical cord	120	19
median uterine artery		
- single	8	2
- both	4	3
common internal iliac artery	56	9

Table 3.1: Arrangement of the experiments and fetal lambs according to the type of occlusion performed.

3.5.1 Umbilical cord occlusions

A device was designed permitting the occlusion of the umbilical arteries and veins, either separately or in combination (de Haan et al., 1976a). It was constructed by the Technical Instruments Department of the Faculty of Medicine and consists of a Teflon framework, measuring 44 x 50 x 18 mm enclosing two semicircular compartments with a diameter of 22 mm each. The weight of this device was 64 grams.
A second, smaller, device also was available, measuring 38 x 45 x 18 mm and weighing 49 grams..

The diameter of the semicircular compartments in this device was 15 mm (fig. 3.1 and 3.2).

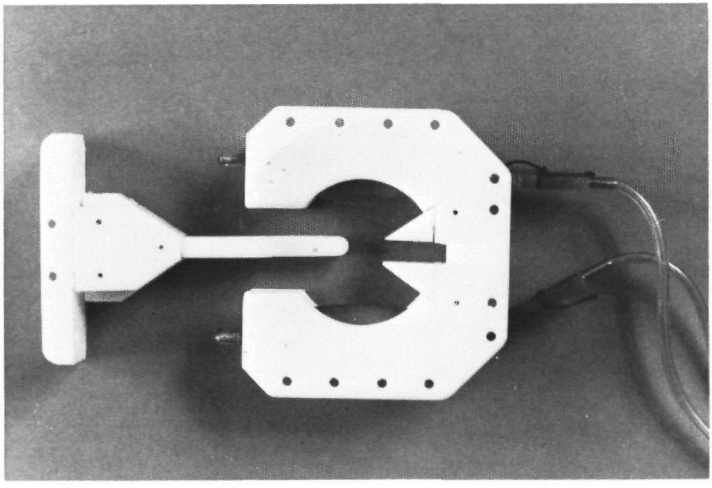


Figure 3.1: Umbilical cord occlusion device, opened, as seen from the fetal side.

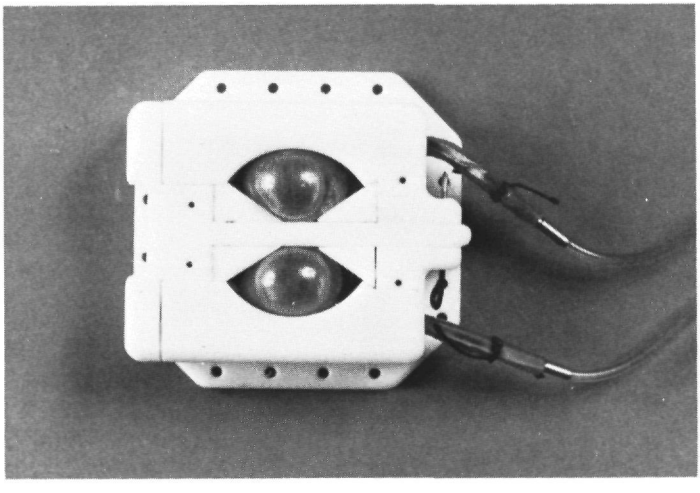


Figure 3.2: Umbilical cord occlusion device, closed, with both occluding balloons inflated. Aspect shown as seen from the placental side.

Each of the two compartments accommodates an inflatable balloon which, after inflation, fills up the total content of the compartment (fig. 3.2).
During the fetal surgery, the cord vessels were separated from one another near the fetal abdominal wall, and the device was assembled around the umbilical cord such that one or more vessels passed through each compartment. Selective occlusion of the vessels in either compartment could thus be performed by inflating the corresponding balloon.
In the cord occlusion experiments the device was positioned around the umbilical cord with the two umbilical arteries in one compartment and the umbilical veins in the other.
By inflating one or both balloons an occlusion could be performed of the umbilical arteries, the umbilical veins or the total umbilical cord. The standard occlusion time in the cord occlusion experiments was , arbitrarily chosen, 30 seconds.
The completeness of the occlusion was ascertained by the change in the phasic flow pattern of an electromagnetic flow transducer positioned around one of the umbilical arteries between the occlusion device and the fetal abdominal wall.
In case of occlusion of the umbilical arteries or of the complete umbilical cord an instantaneous disappearance of the phasic flow pattern was observed (fig. 3.3); in case of occlusion of the umbilical veins a steady decrease in the umbilical artery flow was observed, till after a varying period of occlusion a pendulous flow pattern was observed with zero mean flow (fig. 3.4).
Since simultaneous application of the flowprobe and the occluding device around the cord increased the chance of kinking of the cord by the devices and thus probably of producing a "spontaneous" occlusion, it was decided to abandon the application of a flow transducer after it had been shown in the first few sheep that a complete occlusion of the umbilical vessels was obtained always.

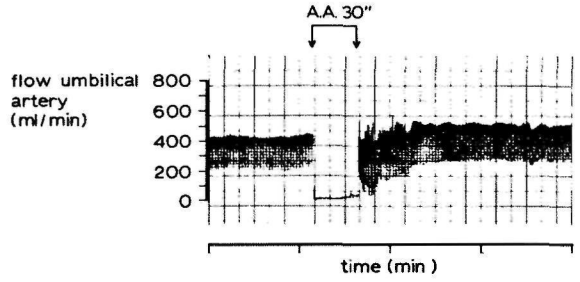


Figure 3.3: Disappearance of the phasic flow pattern of an electromagnetic flow transducer, positioned around one of the umbilical arteries, when the umbilical arteries are occluded.

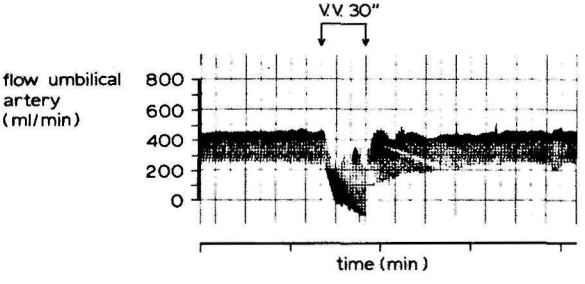


Figure 3.4: Gradual decrease in the phasic flow pattern of an electromagnetic flow transducer, positioned around one of the umbilical arteries, when the umbilical veins are occluded.

3.5.2 Median uterine artery occlusions

Several methods are available to decrease the fetal oxygen supply:

a. Maternal hypotension and/or anemia:
   - depriving the ewe of an amount of blood
   - nypotensive drugs
   - halotnane anesthesia
b. Obstruction of the uteroplacental circulation:
   - infusion of excessive doses of oxytocin resulting in a decrease of intervillous space blood flow
   - infusion of catecholamines
   - partial ablation of the placenta
   - obstruction of the uterine vessels
c. Maternal hypoxemia:
   - in the acute preparation: administering a low oxygen mixture to the mother via endotracheal tube or mask
   - in the chronic preparation: lowering the oxygen content of the inspired air by placing a bag around the ewe's head and ventilating it with low oxygen mixtures

Experiments, based upon provoking changes in maternal cardiovascular and/or respiratory parameters (hypotension, anemia, hypoxemia) were discarded because of the additional poorly controllable effects exerted by endogenous catecholamines upon both the maternal and the fetal cardiovascular system. For the same reason the administration of exogenous pharmacologically active substances (oxytocin, catecholamines) was rejected. Partial ablation of the (cotyledonary) placenta is in the sheep a difficult procedure, requiring extensive surgery. Thus, mechanical obstruction of the uterine circulation remained as the method that appeared to offer the fewest disadvantages.

In a first series of experiments the median uterine artery of the pregnant horn was occluded, using a standard model commercial vessel occluder (Rhodes Medical Instruments,

Inc. Type VO-3), consisting of a flexible Teflon cuff (3 or 4 mm lumen diameter) with an inflatable silicone rubber balloon (fig. 3.5).

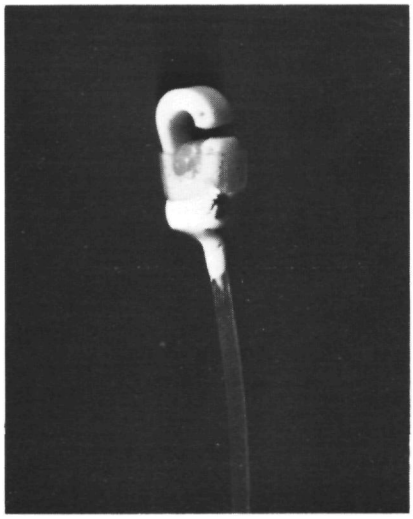


Figure 3.5: Vessel occluder, applied in the median uterine artery occlusions. Situation before application around vessel.

Fluid injected into the device by means of the connecting tubing and a syringe distends the balloon and produces a controllable compression of the vessels contained in the cuff. Deflation is accomplished by withdrawal of the fluid. Although this device was found capable of producing complete occlusion of the median uterine artery, this degree of interruption of the uterine blood supply did not result in an adequate degree of fetal hypoxemia (chapter 5, table 5.9).

A total number of 8 occlusions of a single median uterine artery was performed in two fetal sheep.

Also, occlusion of both median uterine arteries simultaneously could not produce the desired magnitude of change in fetal acid/base balance and blood gas values. Although PO_2 showed a tendency to decrease, this was not accompanied by a change in cardiovascular parameters (chapter 5, table 5.10).

A total number of 4 occlusions of both median uterine arteries was performed in three fetal sheep.

3.5.3 Common internal iliac artery occlusions

Since also total occlusion of both median uterine arteries did not produce a sufficient degree of fetal hypoxemia, the existence of (multiple) arterial anastomoses with other pelvic vessels and/or with the spermatic arteries was postulated.

Hence it was decided to study the collateral connections of the uterine vascular system. For this purpose, in two pregnant ewes that died because of complications of surgery, the internal iliac arteries were exposed. Then the vessels of the pelvis were filled with methylene blue dye, while the median uterine artery at the side of dye injection was occluded.
It appeared that an extensive pattern of anastomoses existed between the vesical plexus (receiving its blood supply from the caudal and cranial vesical arteries) and branches of the median uterine artery.
When both internal iliac arteries were occluded the only possible remaining pathway of uterine blood supply, aside from perhaps some smaller collaterals with the pelvic wall vessels, would be the superior uterine artery, a final branch of the spermatic artery emerging from the abdominal aorta just below the level of the renal arteries. A schematic representation of these findings is shown in figure 3.6.
A search was made to find a location somewhere in the course of the aorta below the renal arteries where a vessel occluder could be fitted. As mentioned before, the best site turned out to be the common part of both internal iliac arteries at the termination of the abdominal aorta just caudal to the place where the two external iliac arteries are given off.

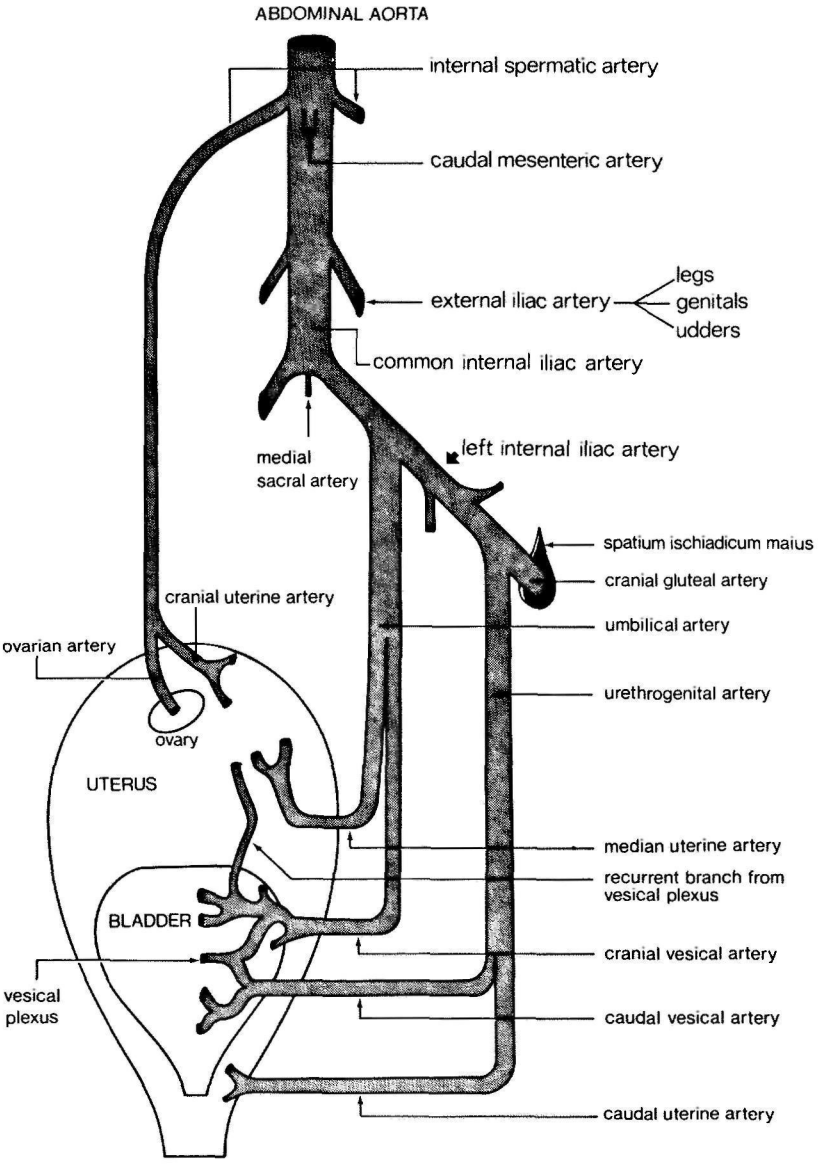


Figure 3.6: Vascularisation pattern of the main pelvic organs in the pregnant ewe of the Dutch sheep, Texel breed.

Occlusion of the uterine blood supply at this level effectuated a fall in fetal arterial PO_2 and pH in all the experiments performed, although the degree of hypoxemia differed from lamb to lamb (chapter 5, table 5.11).
Thus, it was decided to adopt this procedure of occlusion to produce a change in fetal blood gases.

For the occlusion of the common internal iliac artery another type of vessel occluder was applied (Rhodes Medical Instruments Inc., type VO-4), consisting of a flexible silicone cuff lined on the inside surface with inflatable silicone rubber tubing (fig. 3.7).

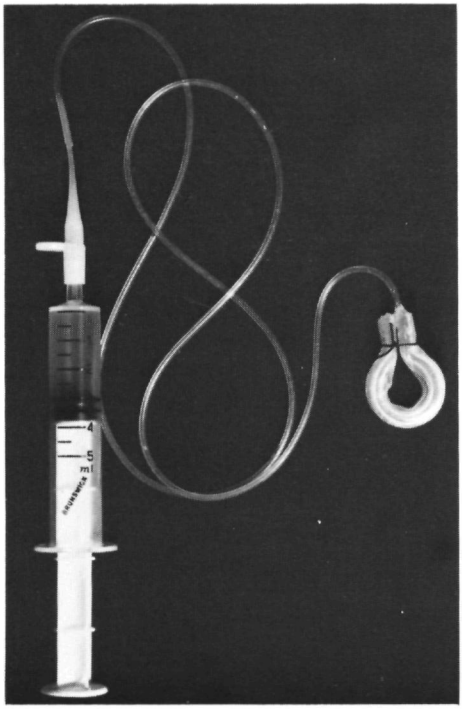
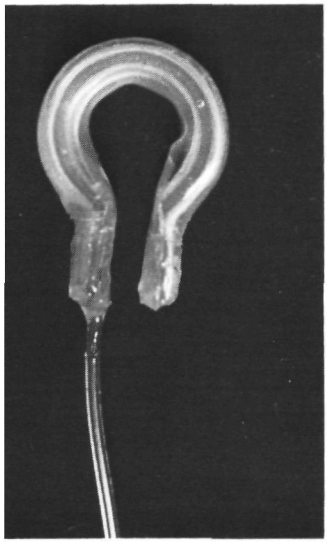
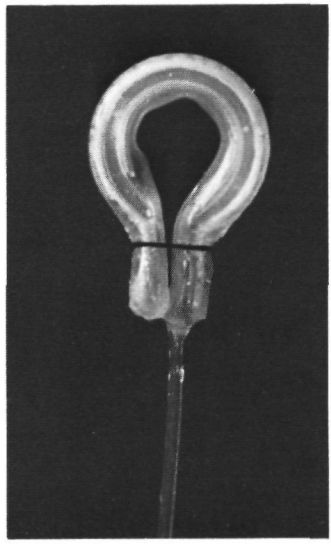


Figure 3.7: Vessel occluder, applied in the common internal iliac artery occlusions, connecting tubing, and syringe for inflation.

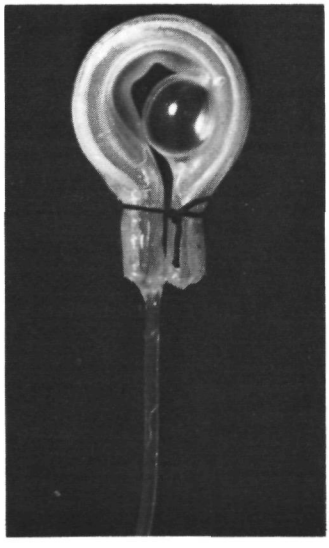
The mode of operation is the same as for the model VO-3 (fig. 3.8 a,b,c). The occluders used had a diameter between 6 and 8 mm.



(a)



(b)



(c)

Figure 3.8:
Vessel occluder applied in the common internal iliac artery occlusions.
a = situation before application around vessel; b = cuff closed by tying a suture; c = balloon inflated.

The degree of occlusion was ascertained by the obliteration of the phasic flow pattern detected by a perivascular electromagnetic flow transducer positioned around one of the median uterine arteries (chapter 5, fig. 5.47).

A total number of 56 occlusion experiments of the common internal iliac artery was performed in 9 fetal lambs.
In contrast to the umbilical cord occlusions which lasted 30 seconds each, the duration of the occlusions of the common internal iliac artery ranged from 0.5 to 30 minutes.
Occlusion of the maternal common internal iliac artery produced a change in fetal cardiovascular parameters after a certain delay time following the onset of the occlusion, which varied among the individual animals.
It is for this reason that the duration of the occlusion was not standardized. Since no continuous PO_2-recording was available, a change in the instantaneously displayed fetal cardiovascular parameters (arterial blood pressure and heart rate) was taken as an index of respiratory/metabolic changes to have taken place.
Once a change in fetal arterial blood pressure and heart rate did occur, a blood sample was drawn and the occlusion released.

Apparently the collateral blood supply varied considerably between the various animals as judged from the variation in occlusion time required to bring about a significant change in fetal respiratory/metabolic and hemodynamic parameters (chapter 5).

3.5.4 Selective autonomic nervous system blockade

In order to get an impression of the role of the various parts of the autonomic nervous system in the response of the fetus to changes induced by both types of occlusion, selective autonomic blockade was accomplished pharmacologically. The blocking drugs were administered intraarterially via the indwelling

catheter. The dosages were determined in relation to the estimated fetal body weight, judged from Naaktgeboren's fetal lamb development scales (Naaktgeboren et al., 1969).
The completeness of the blockade following these dosages was ascertained by inhibition of the effects of the respective agonist in a short series of 18 experiments (table 3.2).

	blocking agent	dose (mg/kg)	agonist	dose (microg/kg)
cholinergic	atropine	1.0	acetylcholine	50
alpha-adrenergic	phentolamine	2.5	norepinephrine	0.6
beta-adrenergic	propranolol	1.0	isoproterenol	0.1

Table 3.2: Drugs and dosages, applied in the present study.

blockade	umbilical veins	umbilical arteries	total cord	common internal iliac artery
cholinergic	8	6	5	6
alpha-adrenergic	4	4	3	6
beta-adrenergic	3	3	2	4

Table 3.3: Arrangement of the various occlusion experiments according to the selective autonomic blockade performed.

The number of the various types of occlusion according to the selective autonomic blockade performed is shown in table 3.3.
The number of animals concerned was small (table 5.7; 5.13). It was only aimed at getting an impression of possible mechanisms involved in the response to the various types of occlusion.

3.5.5 Blood sampling procedure

In order to determine the impact of the various types of occlusion upon the fetal blood gases and the acid/base balance fetal arterial blood samples were drawn at fixed intervals from the indwelling catheter in the fetal aorta.

In umbilical cord occlusion experiments a first (steady state) sample was obtained 5 minutes prior to the start of the occlusion, a second at the very end of the occlusion and a third 5 minutes after the end of the occlusion.

In occlusions of the common internal iliac artery the first sample also was a steady state reference sample.
The second was obtained during the occlusion when fetal respiratory/metabolic changes were supposed to have taken place, judging from the change in cardiovascular parameters (3.5.3).
In two longer-lasting occlusions, SH 1109 and SH 1111, lasting 12 and 30 minutes respectively, additional samples during the occlusion period were obtained (table 5.11).

Since the samples were drawn via the pressure catheter no recordings could be obtained during the period of blood sampling. In order not to interfere with the pressure-tracing, the end-of-occlusion sample was not drawn in the umbilical cord occlusions (table 5.6).

The same applies to some of the common internal iliac artery occlusions, viz. those of a shorter duration.

3.6 Recording equipment

3.6.1 Electrocardiogram and cardiotachogram

A two lead fetal electrocardiogram was obtained from those implanted electrodes providing the most clearly discernible R-waves. The third electrode was used as a reference.
The signals were amplified (Hellige 236 012 04; Hewlett Packard 8811A), displayed (3.6.4) and stored (3.6.5).
The fetal cardiotachogram was obtained from the fetal ECG by a rate computer (MFI-TNO; Hewlett Packard 8812A).
The calculated heart rate was displayed on a strip chart recorder (3.6.4).

3.6.2 Arterial blood pressure

The fetal arterial blood pressure was measured by means of a pressure transducer (Statham $P_{23}Db$; Hewlett Packard 1208C) which was connected to the indwelling femoral catheter by means of an external catheter (length: 180 cm; inner diameter: 1.0 mm; outer diameter: 2.2 mm). The signals from the transducer were amplified (Hellige 206 010; Hewlett Packard 8805B), displayed (3.6.4) and stored (3.6.5).
An electrical calibration of the pressure signal was performed at the beginning and the end of each recording session.
In the course of the experimental period in each fetal lamb, the electrical calibration was compared repeatedly, and if necessary adjusted, to a mechanical pressure gauge.

In order to permit a comparison of results obtained from blood pressure determinations in the various experimental sessions in the same animal, the level of the maternal spine was chosen as point of reference for the position of the pressure transducer. This offers the advantage that an optimal reproducibility of the position of the pressure transducer in respect of the fetal lamb can be obtained.

Locating this point of reference some 15 to 20 centimeters above the level of the fetal heart, however,resulted in fetal arterial blood pressure values some 10 to 15 mmHg lower than those obtained in experiments with the pressure transducer at about the level of the fetus in utero (table 6.2).

3.6.3 Arterial blood flow (fetal/maternal)

The arterial blood flow was measured in one of the fetal umbilical arteries, or in the maternal median uterine artery of the pregnant uterine horn. For this purpose cuff type perivascular electromagnetic flowtransducers (Skalar Instruments, Transflow 800 system) were applied and connected to a matching amplifier (Skalar Instruments, Transflow 601 system, MDL 400). For the umbilical flow measurements, transducers with inside diameters of 3.5 to 4.5 mm were required to provide good electrode contact with minimal vessel constriction. Transducers with an internal diameter of 4 to 6 mm were used to measure the blood flow in the maternal median uterine artery. The flow signals were displayed on a strip chart recorder (3.6.4).

3.6.4 Display of signals

To be able to control the change in cardiovascular parameters directly during the experiments, the FECG, pressure and flow signals, together with the fetal heart rate, were displayed on a direct writing multichannel strip chart recorder (Hellige 218 014; Hewlett Packard 7758A). A marker signal was added to indicate beginning and end of each experimental event.

3.6.5 Storage of signals

FECG, fetal arterial blood pressure and the marker signal also were stored on magnetic tape (Philips Analog 7).
The signals on the tape were subsequently digitized and

analyzed using digital computers (3.8).

3.7 Blood sample analysis

The blood samples, drawn under anaerobic conditions from the indwelling catheter in the fetal aorta, were analyzed either immediately or stored for a short period of time in a refrigerator (+ 4° Celsius), to be analyzed as soon as possible. The delay was never more than 60 minutes.
Analysis was performed by an automatic blood gas analyzer (Corning pH blood gas analyser 165).
This apparatus consisted of a capillary glass electrode for pH measurements, using a calomel electrode as a reference.

PCO_2 was measured by means of a Severinghaus electrode and PO_2 by a Clark electrode.

Base excess was calculated from pH and PCO_2 by a microprocessor unit incorporated in the machine, employing the Siggaard-Andersen nomogram.
Each complete pH and blood gas determination required 175 microliters of whole blood. The instrument was calibrated with fresh buffer and solutions of known O_2 and CO_2 tension before each measurement.
Since only relative changes in pH, PO_2 and PCO_2 due to the occlusion experiments were studied, the differences in measured pH and blood gas values associated with the higher body temperature of the fetal lamb (38-39° Celsius) compared to the 37° Celsius during analysis, were neglected.

3.8 Signal analysis

3.8.1 Data processing

The analog signals stored on magnetic tape, FECG, fetal arterial blood pressure and the marker signal, were filtered (250 Hz lowpass filter) and fed into the analog to digital converter of a computer combination (PDP 11/10 and PDP 11/45). A sampling rate of 500 Hz was used.
Moreover, the FECG also was passed through a band pass filter (15-60 Hz) in order to permit the application of a level detection procedure to the R-wave of the fetal ECG. The output pulse of the level detector was presented to a separate input of the computer, thus supplying each cardiac cycle with a point of reference.
All converted data were stored on disk (and subsequently on magnetic tapes) of the PDP 11/45 computer.
The digitized data were analyzed and the following parameters calculated:

- the fetal heart period or RR-interval, measured as the interval between two successive R-wave reference points.
- the fetal arterial diastolic and systolic blood pressures.
- the PEP.

In the present report the PEP is defined as the time interval between the R-wave reference point and the onset of the upstroke in the fetal arterial blood pressure.
For the onset of this upstroke the maximum is chosen of the approximate second derivative of the pressure signal (cf. Donders et al., 1974), within a given search interval.
The limits of this search interval are dictated by the level crossings at 0.1 and 0.5 of the maximum value in the first derivative of the pressure signal.

3.8.2 Artefact rejection

In the chronic sheep experiment the causes of disturbance in the recorded signals are numerous. Perhaps the most important are the disturbance of the pressure signal by movement of the catheters, either in utero or outside the ewe, and interference with the ECG-signal by electrical muscular activity associated with fetal respiratory and total body movements.

To reduce the amount of inaccurate data the following procedures were applied:

A. *The use of an averaged reference*

At the start of each registration an averaged reference QRS-complex was obtained (64 milliseconds, centered around the R-wave reference point). Every QRS-complex during the succeeding period of registration was compared to this reference complex and its degree of similarity determined (by means of the sum of squares (S) of the differences between corresponding sampling points of the two normalized complexes). The complex was rejected and no related parameters were calculated if the sum S of the complex under consideration varied too much from an empirically determined, preset value.

B. *Range of values*

Other conditions the parameters must meet were:

- the duration of the heart period must exceed 200 milliseconds
- the systolic blood pressure must be between 25 and 150 mmHg, the diastolic one between 7 and 100 mmHg.
- the duration of the PEP must be between 30 and 150 milliseconds

These conditions were used to suppress artefacts. In those (few) cases where these limits were approximated by the original signal, no limits were set.

C. Artefact identification

For each individual parameter supposed artefacts were sifted out if they differed too much from the median value in a given period. For this purpose each period of registration was divided into separate time intervals. The span of these intervals was 10 seconds during the period of cord occlusion and during the first 30 seconds following the occlusion. During the remaining part of the registration and during the complete duration of registration in the case of an iliac artery occlusion, the time intervals were 30 seconds each. For each parameter the median during the respective time interval was calculated.

Those values that both differed more than 20% from this median value and exceeded the interval between $P_{50} - 2 (P_{50} - P_{12.5})$ and $P_{50} + 2 (P_{87.5} - P_{50})$, were discarded (P = percentile).

In case of less than 11 parameters being present in the respective time interval, the latter condition was changed into: $P_{50} - 3 (P_{50} - P_{25})$ and $P_{50} + 3 (P_{75} - P_{50})$.

Moreover, the efficiency of this artefact identification program was checked on the basis of a graphical representation and unsatisfactory results were corrected.

3.8.3 Data reduction

For statistical testing the data were further reduced.
To this aim each individual recording period was divided into subintervals during which the median value of each parameter was calculated together with its interquartile range.
These subintervals consisted, in case of an umbilical cord occlusion, of a 30 seconds initial control steady state registration and 3 intervals each lasting 7.5 seconds.
The first covered the first 7.5 seconds of occlusion, the second the last 7.5 seconds of occlusion and the third a period of 7.5 seconds at a moment 30 seconds following the end of occlusion.

The 30 seconds steady state period was also in case of a common internal iliac artery occlusion the first subinterval. It was followed by three further intervals, each lasting 15 seconds. The first was preceding the moment of blood sampling during the occlusion and the second was immediately following the end of this blood sample. The last interval was chosen at 60 seconds following the end of the occlusion.

CHAPTER 4

EVALUATION OF THE PEP MEASUREMENT

In this chapter the individual factors that might influence the determination of the PEP will be discussed.
A comparison will be made between the accuracy of a manual PEP-measuring method and the automatized processing method used in the present study.

4.1 Factors influencing the PEP-measurement

Measurement of the PEP, defined as the time interval between the Q-wave in the fetal ECG and the onset of aortic blood pressure rise, inevitably involves some sources of possible variance when comparing the results of PEP-determinations in two fetal lambs or even in the same animal on two different occasions.
Since in this study the beginning of the pre-ejection period, i.e. the Q-wave, is substituted by a fixed trigger point in the QRS complex, the factors affecting the determination of this point were investigated. Also factors influencing the determination of the end of the PEP, i.e. the onset of aortic blood pressure rise, were studied.

4.1.1 Determination of the onset of the pre-ejection period

Two kinds of variables can be discerned in the determination of the fixed trigger point in the QRS complex: those introduced by a (patho)physiologic change in the QRS complex, and those determined by the technical procedures applied to calculate the exact moment of triggering.

4.1.1.1 (Patho)physiological factors affecting the determination of the onset of the PEP

The method of level detection, applied to determine the trigger point in the QRS complex, yields a point between the onset and the end of the R-wave in the fetal ECG, depending on the moment that the rising leg of the filtered R-wave crosses the preset trigger level. This procedure can be influenced by a (patho)physiologic change in the QRS complex form during the period of registration. An artefact indication procedure was incorporated in the signal-analyzing program, indicating possible aberrant QRS complexes (e.g. extrasystoles) and QRS complex changes in the course of each individual period of registration (chapter 3.8.2).

4.1.1.2 Methodologic/technical factors affecting the determination of the onset of the PEP

Three inconsistencies in the trigger point determination can be attributed to technical variability:

- Interchanging of the ECG-leads and the reference electrode will bring about the possibility of a change in QRS complex and thus of trigger point localization with each successive period of registration. This was prevented by labeling the individual ECG lead electrodes and standardization of the leads applied, once the configuration of leads for an optimal QRS complex form had been determined in case of the fetal lamb at issue.
- By changing the polarity of the filtered ECG signal the moment of level crossing of the band-passed R-wave and thus the trigger point will be shifted.
- By changing the amplitude of the filtered ECG-signal, the trigger level may be intersected at a different moment during the QR-interval, bringing about a shifting of the trigger point.

The first two factors of possibly inaccurate PEP determination will be of importance only when results are compared that are obtained on different occasions. Since in the present investigation only PEP changes within one uninterrupted period of registration are concerned, they can properly be neglected.

The third factor, a change in the moment of level crossing of the filtered R-wave due to an alteration in the amplitude of this signal will produce a possible error of less than 2 milliseconds. It thus lays within the measuring error, amounting 2 milliseconds, given the sample frequency of 500 Hz. Besides, to much shifting of the trigger point will be identified by the artefact rejection procedure.
The impact of the combined error of all three above-mentioned factors of inconsistency upon the determination of the duration of the PEP was calculated. For this purpose the distance between the Q-wave and the trigger point was manually measured in 30 processed registrations from different fetal lambs:

Q-trigger point interval:	m $\pm$ S.D.	= 15.6 $\pm$ 1.4	msec
	median	= 16	msec
	range	= 13 - 18	msec

An obvious lag time could be registered between the Q-wave and the trigger moment, but this lag time turned out to be remarkably constant as reflected by a standard deviation of 1.4 msec and a range of 5 msec. On theoretical grounds this range can not exceed 10 msec.

4.1.1.3 Conclusions

The trigger point, as determined by the level detection procedure, shows an obvious but constant time delay following the Q-wave, of 15.6 $\pm$ 1.4 msec (m $\pm$ S.D.).
The constancy of this time delay led to the decision not to correct the PEP for changes induced by substituting the Q-wave

by the trigger point. Besides, when determination of the exact pre-ejection period is wanted, the "triggered" PEP can be turned into a "real" PEP by adding the measured lag time between Q-wave and trigger point to every measured value of the "triggered" PEP. The lag time can be calculated in each individual registration.
In order to avoid artificially induced QRS complex changes care was taken to mark the electrodes used as leads and reference in obtaining the fetal electrocardiogram.
(Patho)physiologically induced QRS complex changes during the experimental period were detected by an artefact indication program. Apart from some single aberrant QRS complexes, that could be skipped without loosing too much information, of 268 registrations only two had to be discarded because of considerable persistent QRS complex changes during the period of registration. In fact, in the literature, the changes in the fetal electrocardiogram, observed during fetal distress probably due to cardiac tissue hypoxia, appear to consist mainly of changes in P-wave, PQ-interval, ST-segment and/or T-wave (Pardi et al., 1974).
An exception occurs in fetuses affected by slowly progressive fetal distress in severe forms of hemolytic disease due to Rhesus iso-immunization. In these cases the QRS complex duration becomes chronically prolonged (Brambati et al., 1976).

4.1.2 Determination of the end of the pre-ejection period

The registration of the arterial blood pressure was performed by means of a pressure transducer connected to a fluid filled catheter threaded forward into the aorta.
Two kinds of variables must be taken into account when discussing the factors influencing the determination of the end of the PEP: (Patho)physiological changes of the pulse wave form and methodological/technical errors in the determination of the moment of onset of aortic blood pressure rise.

4.1.2.1 (Patho)physiological factors affecting the determination of the end of the PEP

Differences in the registration of the onset of aortic blood pressure rise, the end of the PEP, originating from the physiological properties of the cardiovascular system predominantly consist of alterations in the velocity of pulse wave propagation from the aortic valve to the tip of the catheter.
The transmission velocity of the pulse wave in a blood vessel is determined largely by the distensibility (D) of the vascular wall ($D = \frac{\Delta V \times 100}{\Delta P \times V}$).
Bramwell and Hill (1922) developed a formula for pulse wave velocity:

$$v = K\sqrt{V.\frac{\Delta P}{\Delta V}} \qquad m/sec$$

Were v is pulse wave velocity, V is the initial vessel volume, ΔV is the increment in volume, ΔP is the increment in pressure and K is a constant (Bramwell and Hill, 1922).

In the absence of vascular disease (a very rare finding in the fetus), the pulse wave velocity in the aorta thus will be determined mainly by the vessel wall stiffness and the vessel volume (Wiggers, 1952), which, in turn, depend upon such variable factors as blood pressure, autonomic nervous tone, vasodilatation and levels of circulating catecholamines.
A rise in blood pressure or adrenergic stimulation will not only exert an influence upon the pulse wave velocity by changing the volume of the vessel, but also will affect the pulse propagation time by distending and acting upon the tone respectively of the vessel wall. A rise in arterial blood pressure due to umbilical cord occlusion or to an increase in the total systemic resistance, will result for example in an increase of vessel volume and of vessel wall tension, which means a decrease in compliance, causing in turn a rise in pulse wave velocity.

Landowne (1958) showed in adult human subjects that an increase in arterial systolic blood pressure of 25 mmHg, comparable to the increase in fetal blood pressure during umbilical cord occlusions, resulted in an increase of pulse wave velocity of 2.5 m/sec, independent of the initial arterial blood pressure and pulse wave velocity.
The degree to which the pulse wave velocity increase during a rise in blood pressure influences the PEP-determination in the fetal lamb can not be determined exactly, but since the effect (to shorten the PEP) only occurs during a rise in afterload (which is known to prolong the PEP), the negative influence of the occlusion upon the pulse propagation time was not taken into account. Moreover, even in the extreme case of doubling the fetal arterial blood pressure from 75 to 150 mmHg, an initial pulse wave velocity as slow as 5 m/sec, and a distance between aortic valve and catheter tip as long as 10 cm, the change in the PEP would not exceed 12 msec according to Landowne's figures for humans.

In addition, the pulse wave transmission time also depends on the absolute distance from the aortic valve to the tip of the catheter. This distance will not only vary between the various fetuses, but theoretically it will also increase with growth of the fetal lamb during the experimental period, should this last more than a few days. Between 120 and 147 days of gestational age the fetal lamb grows (crown-rump length) from 35 to 45 cm (Naaktgeboren et al., 1969).
If this growth is distributed evenly throughout all parts of the fetal body, this will result for the aorta in an increase of length of about half the total increase (0.5 x 10 = 5 cm). At an assumed pulse wave velocity of 5 m/sec, this will result in an increase of the pulse propagation time of 2.5 msec/week; while at a pulse wave velocity of 10 m/sec, the increase in pulse propagation time during the last 4 weeks of gestation would be 5 msec, equivalent to 1.25 msec/week.

4.1.2.2 Methodological/technical factors affecting the determination of the end of the PEP

The problem arising when catheters have to be chosen that can be used to conduct the pulse wave to the pressure transducer, is that a compromise has to be sought between an optimal signal, i.e. the pulse wave form, being transmitted without substantial delay, which requires a solid, stiff catheter with a wide diameter, that can't be squeezed, and, on the other hand, a catheter which is small enough to fit into the peripheral femoral artery of even the youngest lamb fetus and flexible enough to be bended without kinking.

It is obvious from the Bramwell and Hill equation cited earlier (chapter 4.1.2.1) that in a wide, rigid catheter the impact of ventricular ejection would be transmitted almost instantly to the surface of the pressure transducer, once it has arrived at the tip of the catheter (Bramwell et al.,1922). As a result of a preliminary investigation two polyvinyl catheters were chosen to be used in this study:

- A flexible internal catheter that would be inserted in the fetal aorta via the incision in its hindlimb vessel. The dimensions of this catheter (length x inner diameter x outer diameter) were: 150 x 0.08 x 0.16 cm. The delay in pulse wave propagation time of this catheter amounted to 25 msec.
- A rigid external catheter that would be applied to connect the internal one to the pressure transducer. The dimensions of this catheter (length x inner diameter x outer diameter) were: 180 x 0.10 x 0.22 cm. The delay in the pulse wave propagation time of this catheter amounted to 15 msec.
- The pulse wave propagation time in the complete system applied in the fetal blood pressure registration, internal catheter, external catheter plus connecting pieces, was 40 msec.

Other catheter types had been rejected either because their flexibility was insufficient for use during chronic experiments, or because the pressure wave form was altered unacceptably.

4.1.2.3 Conclusions

- The delay of the pulse transmission time in the aorta includes the most variable part of the PEP as it is determined in the present investigation. At a gestational age of 120 days and a fetal crown-rump length of about 35 cm the distance between the heart and the bifurcation of the femoral artery will be about 30 cm. At 147 days (term) the fetal lamb will measure 45 cm and the distance heart-femoral artery about 35 cm.
  Since it is not possible to determine exactly the distance from the catheter tip to the aortic valve, it is here that much uncertainty will remain. The earlier mentioned growth-depending increase of the PEP by about 1 to 2 msec per week has to be taken into account when the PEP is evaluated as a parameter of worsening fetal condition and also is likely to interfere with the real PEP-increase during in utero life, the latter probably due to growth of the fetal heart and thus of the time needed to accomplish a complete depolarization of the ventricles (Murata et al., 1978a).
- Beside the strong positive correlation of the PEP with the heart's afterload a simultaneous slight negative effect can be expected from the increase in pulse wave velocity induced by a rise in fetal arterial blood pressure.
- The possible systematic and random errors inherent to the method of measuring the PEP applied are listed in table 4.1 together with their significance in regard to the applied method of PEP determination.
- It was concluded to standardize ECG-leads, pressure transducers and catheters, and also to aim at a standardization of the distance between heart and catheter tip, i.e. the

distance the catheter is threaded forward into the aorta.

source	code	error	size (msec)	prevented by
gradual changes QRS complex	R	syst.	5-10	'artefact'rejection
changing amplitude QRS complex	R	rand.	< 2	negligible
changes pulse wave velocity	R	syst.	12	
interchanging ECG leads	S	syst.	13-18	labeling electrodes
different polarity trigger level	S	syst.		
substitution Q-wave by trigger	S	syst.		adding lag time
increase distance Ao.v.-tip cath.	S	syst.	2.5/wk	
distance Ao.v.-tip catheter	SS	syst.	30	standardization
choice of catheter	SS	syst.	50	standardization

Table 4.1: Possible error sources in the method of PEP-measurement. Detailed description in text. 'code' indicates whether the error source at issue applies to a comparison of results obtained on different occasions in different fetal lambs (SS), or also to a comparison of results obtained on different occasions in one single fetal lamb (S), or even of results obtained in one single period of registration in one fetal lamb (R). 'size' indicates the maximal magnitude of the possible error. All error sources marked SS and S do not apply to a comparison of results obtained in one single registration period only and are thus not of importance in regard of the present investigation, which only deals with a comparison of relative changes in the PEP as measured during separate periods of registration in one fetal lamb. 'syst.' and 'rand.' indicate the systematic or random character of the individual error sources. 'Ao.v.' = aortic valve; 'cath.' = catheter.

In evaluating the accuracy of the PEP-measurement as performed by the automated signal analysis program, the problem of a validated reference standard is encountered.
Standard PEP does not exist, and measuring the PEP manually from high-speed (200 mm/sec) FECG and blood pressure recordings involves a good deal of inaccuracy of its own due to the difficulty of localizing exactly the onset of the upstroke in the blood pressure tracing.
A comparison of the specific features of both methods can be made from figure 4.1 where the PEP is plotted as measured both manually and by the computer program during an experiment involving the occlusion of both umbilical veins. Regarding the manually measured PEP, the "real" PEP is considered, i.e. the interval between the Q-wave in the FECG and the onset of the upstroke in the arterial blood pressure tracing.

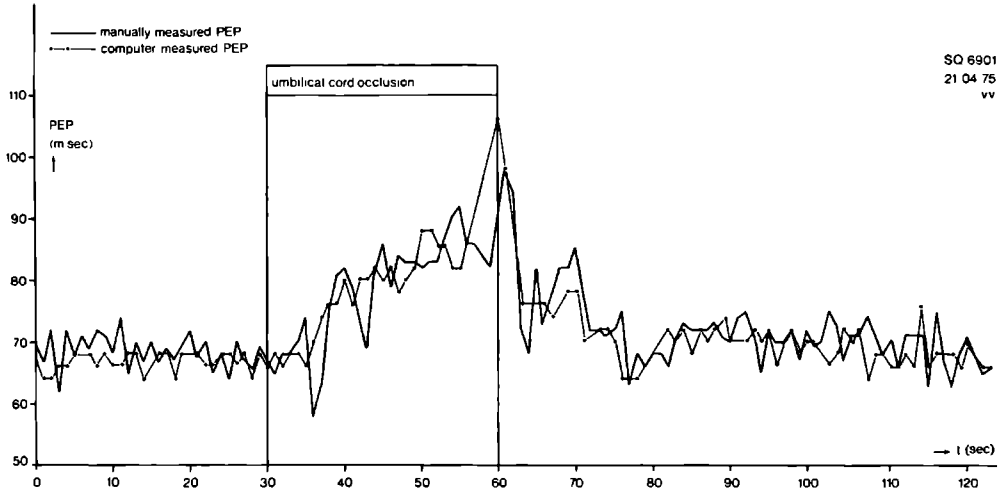


Figure 4.1: Comparison of the PEP measured manually and by the automated signal analysis program. Occlusion of both umbilical veins, indicated between the two vertical bars, in exp. no. SQ 6901. Duration of the PEP (in msec) on the ordinate, time (in sec) on the abscissa.

The computer-calculated PEP tends to be somewhat shorter than the manually measured one. Moreover, the band-width of the manually measured parameter is broader than that of the computer-calculated one. This, presumably, represents the smaller precision that can be attained in the determination of the exact onset of the upstroke in blood pressure by the manual measurement method.
The mean value for the determination of the PEP during a 60-second period of steady state registration obtained by the manual method was compared to the computer-calculated one:

"manual" PEP	: 68.6 ± 2.8	msec (m ± S.D.)
	69	msec (median)
	62 - 74	msec (range)
"automated" PEP	: 66.9 ± 1.6	msec (m ± S.D.)
	66	msec (median)
	62 - 70	msec (range)

Thus during this period there was an average time lag between both methods of 1.7 msec, the automated method yielding shorter PEP's.
This average time lag ranged from -1 to 12 msec in the 41 experiments in 8 fetal lambs where it was calculated by both methods simultaneously, yielding an overall average time delay of 5.3 ± 3.8 msec (m ± S.D.), the manually measured PEP being longer.
The smaller standard deviation of the "automated" PEP in every registration suggests a superiority of this method over the manual one with regard to the accuracy of the PEP determination.
Apparently also the automated upstroke detection in the fetal arterial blood pressure is lagging some milliseconds behind the actual onset of pressure rise, since, had both moments coincided, the earlier measured difference of 13-18 msec,

originating from the substitution of the Q-wave by the QRS trigger point, would also have been found here.

CHAPTER 5

RESULTS

5.1 Steady state registrations

On each day during the experimental period, whether or not an experiment was scheduled, steady state values were determined for acid/base balance and blood gas tensions, simultaneously with a registration of the various cardiovascular parameters during the same conditions.

5.1.1 Steady state values of acid/base balance and blood gases

The results of the steady state blood sample analyses are listed in table 5.1.

n	212	
pH	7.37 ± 0.06	
PO_2	2.8 ± 1.0	kPa *
PCO_2	5.8 ± 1.0	kPa

Table 5.1:
Fetal arterial blood gases and acid/base balance in non-stressed steady state conditions (m ± S.D.).

No significant changes in blood gas tensions and pH were observed following the administration of selective autonomic blocking agents to the fetal lambs. For this reason all steady state results were grouped together in table 5.1. The mean pH was calculated by converting every single pH into its corresponding hydrogen ion concentration. The hydrogen ion concentrations were averaged and the mean concentration reconverted into the "mean pH".

* 1 kPa = 1 kiloPascal = 1 N/m^2 = 7.5 mmHg

The same procedure was applied in calculating the standard deviation of the pH.

5.1.2 Steady state values of cardiovascular parameters

The steady state cardiovascular parameters in fetal lambs with an intact autonomic nervous system are shown in table 5.2. The results obtained following blockade of part of the autonomic nervous system were not entered in this group.

n	163
systolic blood pressure	61 $\pm$ 14 mmHg
diastolic blood pressure	36 $\pm$ 9 mmHg
R-R interval (heart rate)	372 $\pm$ 62 msec (161 bpm)

Table 5.2: Fetal cardiovascular parameters during non-stressed steady state conditions in fetal lambs with intact autonomic nervous systems (m $\pm$ S.D.).

5.1.3 Blockade of parts of the autonomic nervous system

Atropine, phentolamine or propranolol were employed in individual experiments to block, respectively, the cholinergic (parasympathetic) and alpha- or beta-adrenergic (sympathetic) autonomic influences on heart rate, myocardial contractility and vascular tone.
The administration of one of these pharmacologic blocking agents was accompanied by a change in the steady state levels of one or more hemodynamic parameters. By means of analysis of variance no animal dependency of the results could be demonstrated (every separate p-value above 0.125).
The effects of the administration of atropine upon the steady state levels of fetal systolic and diastolic blood pressure, pre-ejection period and heart period could be studied on 10 different occasions in 5 fetal lambs (table 5.3).

	BEFORE ATROPINE				AFTER ATROPINE			
SH	sys (mmHg)	dias (mmHg)	PEP (msec)	RR (msec)	sys (mmHg)	dias (mmHg)	PEP (msec)	RR (msec)
1514	49	26	70	416	49	31	100	354
1526	58	35	102	414	87	60	85	366
6905	63	35	68	330	67	37	61	354
6910	60	33	51	429	57	36	54	329
6913	63	38	52	388	66	38	52	387
7806	58	33	65	355	62	38	60	325
8206	53	29	63	455	51	29	72	486
8216	64	36	77	414	67	39	74	354
8219	63	38	83	461	62	37	78	390
9308	67	35	67	372	70	37	69	332

Table 5.3: Fetal cardiovascular parameters in non-stressed steady state conditions before and after the administration of atropine. Median values are given. SH = experiment code number; sys = fetal arterial systolic blood pressure; dias = fetal arterial diastolic blood pressure; PEP = pre-ejection period RR = heart period.

	m ± S.E.M.	t - test
systolic blood pressure (mmHg)	+ 4 ± 3	N.S.
diastolic blood pressure (mmHg)	+ 4 ± 1	$p < 0.05$
PEP (msec)	+ 1 ± 4	N.S.
R-R interval (msec)	- 36 ± 13	$p < 0.025$

Table 5.3a: Fetal cardiovascular parameter changes induced by the administration of atropine. m = mean change; S.E.M. = standard error of the mean; p = tail probability; N.S. = not significant ($p > 0.05$).

The significance of the differences in steady state cardiovascular parameters induced by the administration of atropine were evaluated by Student's t - test for paired observations (table 5.3a). The increase in fetal arterial diastolic blood pressure and the decrease in R-R interval duration reached levels of statistical significance in these fetal lambs (gestational ages : 129 -147 days).

The effects of the administration of the alpha-adrenergic blocking agent phentolamine were studied on 6 different occasions in 4 fetal lambs (table 5.4). The gestational ages ranged from 120 to 134 days.

	BEFORE PHENTOLAMINE				AFTER PHENTOLAMINE			
SH	sys (mmHg)	dias (mmHg)	PEP (msec)	RR (msec)	sys (mmHg)	dias (mmHg)	PEP (msec)	RR (msec)
0704	50	33	89	346	46	31	80	349
1103	37	22	114	342	35	21	102	308
1507	50	29	80	410	45	29	80	331
1516	47	25	98	412	40	22	77	315
9911	53	32	119	389	49	34	111	341
9913	61	37	114	436	52	36	118	304

Table 5.4: Fetal cardiovascular parameter determinations in non-stressed steady state conditions in fetal lambs before and after the administration of phentolamine. (Abbreviations as in table 5.3).

Sheep codes starting with the digits 99 represent experiments in the fetal lamb of ewe 69-77, those starting with 69 are from the lamb of ewe 69-75.

	m ± S.E.M.	t - test
systolic blood pressure (mmHg)	- 5 ± 1	p = 0.005
diastolic blood pressure (mmHg)	- 1 ± 1	N.S.
PEP (msec)	- 8 ± 4	N.S.
R-R interval (msec)	- 65 ± 20	p < 0.025

Table 5.4a: Fetal cardiovascular parameter changes induced by the administration of phentolamine. Legends of table 5.3a.

Student's t - test was employed to evaluate the changes induced by phentolamine (table 5.4a).
The decreases in systolic blood pressure and R-R interval reached the level of statistical significance.

The effects of the administration of the beta-adrenergic blocking agent propranolol were studied on 6 different occasions in 3 fetal lambs (table 5.5). Gestational ages ranged from 126 to 132 days.

	BEFORE PROPRANOLOL				AFTER PROPRANOLOL			
SH	sys (mmHg)	dias (mmHg)	PEP (msec)	RR (msec)	sys (mmHg)	dias (mmHg)	PEP (msec)	RR (msec)
0703	51	39	90	296	53	35	87	423
1510	58	34	74	376	51	32	83	443
1519	49	26	99	431	55	29	96	433
9901	47	31	98	408	68	36	97	385
9908	58	36	110	369	54	31	109	404
9910	53	32	119	389	61	39	123	393

Table 5.5: Fetal cardiovascular parameters in non-stressed steady state conditions before and after the administration of propranolol. (Abbreviations as in table 5.3).

	m ± S.E.M.	t - test
systolic blood pressure (mmHg)	+ 5 ± 4	N.S.
diastolic blood pressure (mmHg)	+ 1 ± 2	N.S.
PEP (msec)	+ 1 ± 2	N.S.
R-R interval (msec)	+ 35 ± 22	N.S.

Table 5.5a: Fetal cardiovascular parameter changes induced by the administration of propranolol. Legends of table 5.3a.

None of the changes induced by the administration of propranolol in either the steady state values of the systolic blood pressure, the diastolic blood pressure, the PEP or the R-R interval, was statistically significant, according to Student's t-test for paired observations (table 5.5a).

5.1.4 Summary of observations

- Non-stressed steady state levels were determined for fetal blood gases and cardiovascular parameters.
- No change was found in fetal pH, PO_2 and PCO_2 following a selective blockade of the individual components of the autonomic nervous system.
- Administration of atropine was followed by a significant rise in steady state heart rate levels ($p < 0.025$; Student's t-test for paired observations). A significant change also occurred in the fetal diastolic blood pressure ($p < 0.05$; Student's test). No significant change was found in systolic blood pressure and PEP.
- Administration of phentolamine was followed by a significant rise in fetal heart rate ($p < 0.025$; Student's test), whereas the fetal arterial systolic blood pressure fell ($p = 0.005$; Student's test). There was no consistent change in the

diastolic blood pressure, nor in the duration of the PEP.

-Administration of propranolol was followed by a fall in fetal heart rate, which however failed to reach statistical significance. No significant change was found either in fetal systolic or diastolic blood pressure, nor in the PEP.

5.2 Umbilical cord occlusions

The placenta serves as the exchange organ between the fetal and maternal circulation for oxygen and metabolizable nutrients as well as for respiratory and metabolic wastes.
Occlusion of either the afferent or the efferent vessels of the fetal placental circulation will bring about a change in fetal blood gases and acid/base balance. Moreover, since about 40-45% of the combined ventricular output is distributed to the fetal placental circulation (Rudolph, 1970; Peeters, 1978), obstruction of the placental vascular bed will result in an increase in the total peripheral resistance.
Moreover, a decrease in venous return from the placenta may also lead to a disturbance of the fetal hemodynamic equilibrium.
The respiratory/metabolic changes induced by the occlusion of the umbilical circulation will be referred to as biochemical changes (5.2.1); and those involving fetal hemodynamic disturbances, as hemodynamic changes (5.2.2).

5.2.1 Biochemical changes

As stated earlier (section 3.5.5), in order not to interfere with the pressure recording at a most important moment of the occlusion, a sample at the very end of the 30-second occlusion was obtained only during 11 experiments in 3 fetal lambs. The biochemical changes in these experiments are summarized in table 5.6.

For statistical analysis the assumptions mentioned in appendix I were made. Besides, it was assumed that the biochemical changes measured during the occlusions were not influenced by the type of occlusion performed (both umbilical arteries, both veins or the complete umbilical cord).
The changes were measured as: sample end-of-occlusion minus sample before occlusion (= changes during occlusion) and sample after minus sample end (= changes following occlusion).

SH	5 min before occlusion			end of occlusion			5 min after occlusion		
	pH	PO_2 (kPa)	PCO_2 (kPa)	pH	PO_2 (kPa)	PCO_2 (kPa)	pH	PO_2 (kPa)	PCO_2 (kPa)
9601	7.40	2.8	7.3	7.34	2.3	5.2	--	--	--
9602	7.39	3.1	6.6	7.37	2.5	6.6	--	--	--
9603	7.39	2.7	4.5	7.38	1.8	4.3	7.23	2.2	5.0
9604	7.42	2.7	5.7	7.40	1.9	6.3	7.40	2.9	5.7
9605	7.41	3.0	5.6	7.39	1.9	6.2	7.39	2.8	5.1
9606	7.40	2.7	7.0	7.41	--	--	7.39	2.7	5.0
9607	7.33	2.6	7.1	7.31	1.6	6.7	7.27	2.8	6.5
9801	7.41	2.7	6.0	7.38	2.0	7.1	7.36	2.5	7.1
9802	7.39	2.9	5.4	7.39	2.2	5.1	7.25	2.0	6.8
9701	7.24	2.4	6.9	7.24	2.2	7.1	7.23	2.6	6.9
9702	7.35	2.0	5.9	7.34	1.7	6.1	7.29	2.2	6.3

Table 5.6: Biochemical changes induced by the occlusion of the umbilical circulation during 11 experiments in 3 fetal lambs with intact autonomic nervous systems; kPa = kiloPascal.

No animal dependency could be demonstrated, by means of analysis of variance, regarding the pH changes produced by the occlusion. The mean decrease in pH during the occlusion (- 0.02), as well as the continuing fall after the end of the occlusion (- 0.05) both were statistically significant ($p < 0.05$ Student's test for paired observations).

Regarding the PO_2 changes during the occlusion an animal dependency was demonstrated by means of analysis of variance, whereas no such dependency could be demonstrated for the PO_2 changes during the post-occlusion period; the tail probability however was small ($p = 0.13$). The mean fall in PO_2 during the 30-second occlusion was - 0.6 kPa; during the post-occlusion phase a partial recovery was seen (+ 0.5 kPa). No reliable testing could be performed under these conditions. Separate

analysis of the results obtained in the fetal lamb of ewe 96-77, however, showed the PO_2 at the end of the occlusion to be significantly lower than before, whereas the post-occlusion sample revealed a PO_2 which was significantly higher than the one measured in the end-of-occlusion sample ($p = 0.0003$ and $p = 0.014$, respectively; Student's test for paired observations).

No animal dependency could be demonstrated regarding the changes in PCO_2 during and after the occlusion.
Regarding the PCO_2 no consistency was observed in the changes during the occlusion, nor during the post-occlusion period.
On neither of the two occasions the mean change was statistically significant ($p > 0.05$).

5.2.2 Hemodynamic changes

Occlusions were performed of either the two umbilical arteries, or the two umbilical veins, or the complete umbilical cord, both in fetal lambs with intact autonomic nervous systems and during selective pharmacologic blockade of parts of this system.

A total number of 120 umbilical cord occlusion experiments has been performed in 19 fetal lambs.
Eighty-four of these yielded both technically suitable tracings and reliable blood sample analyses: 35 involved occlusion of both umbilical veins; 26, occlusion of both umbilical arteries; and 23, occlusion of the complete umbilical cord.

The reasons for exclusion of an experiment from the data analysis were technical failures (broken ECG-electrodes, blocked pressure catheter, missing marker signal, recording errors), 32 times; failed blood sample, 14 times; incomplete occlusion due to leakage of the occluding balloon, 3 times;

occlusion lasting over 30 seconds due to failure to empty balloon in time, 3 times.

5.2.2.1 Intact autonomic nervous system

In fetal lambs with intact autonomic nervous systems 46 suitable tracings of occlusion experiments have been obtained together with reliable blood sample analyses.
Twenty involved occlusion of both umbilical veins, 13 times the umbilical arteries were occluded, and 13 times a complete cord occlusion was performed.

5.2.2.1.1 Occlusion of both umbilical arteries

During occlusion of both umbilical arteries (code: AA), fetal systolic and diastolic arterial blood pressure rose immediately following the onset of the occlusion in every experiment performed. Simultaneously, the fetal heart rate decreased. Both phenomena are shown in figure 5.1.
The level of systolic and diastolic blood pressure reached after the initial rapid rise was either maintained during the remaining part of the occlusion, or was followed after some delay by a second steep increase. This phenomenon, the second rise in systolic and diastolic blood pressures, which also can be observed in figure 5.1, will be discussed in section 5.2.2.1.4.

In none of these chronic experiments with intact autonomic nervous system a fall was observed in fetal arterial systolic or diastolic blood pressure during the period of occlusion.

Fetal heart rate changes during the second part of the occlusion were less consistent.
Both a continuing slow fall in heart rate until the end of the occlusion or a partial recovery could be observed.
As can also be seen in figure 5.1, the recovery of the fetal

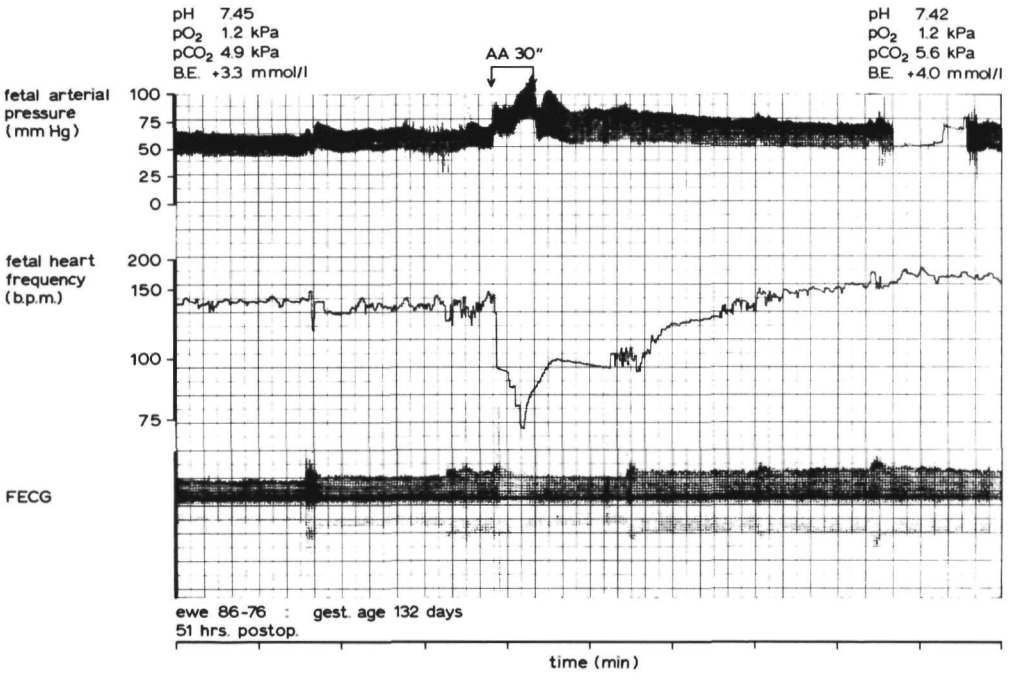


Figure 5.1: Occlusion of both umbilical arteries (AA) for 30 seconds (30") in the fetal lamb of ewe 86-76. Results of blood sample analyses 5 minutes before and 5 minutes after the occlusion are indicated at the top of the figure.

heart rate was only partial.
Such a partial recovery of fetal heart rate occurred notwithstanding the further rise in fetal arterial systolic and diastolic blood pressure.
Further processing of the data (chapter 3.8) permitted a more detailed study of the hemodynamic changes induced by the occlusion of the umbilical arteries.

Figure 5.2 shows the changes in systolic blood pressure during occlusion of both umbilical arteries (AA) in experiment number 5 in the fetal lamb of ewe number 78 (code: SH 7805).
The instantaneous initial pressure rise as well as the second step rise after about 15 seconds of occlusion can be observed.

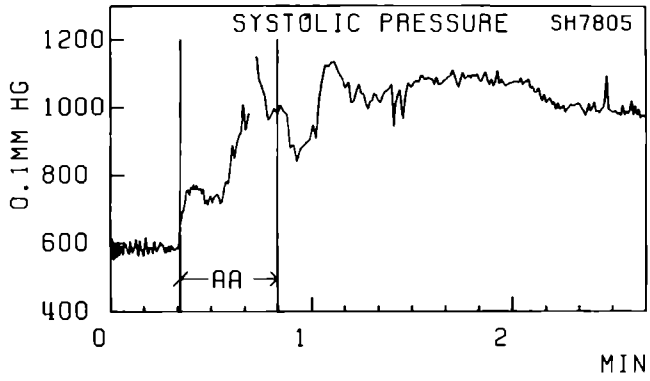


Figure 5.2: Occlusion of both umbilical arteries (AA) indicated by the two vertical bars; experiment no. 5 in the fetal lamb of ewe 78-75.

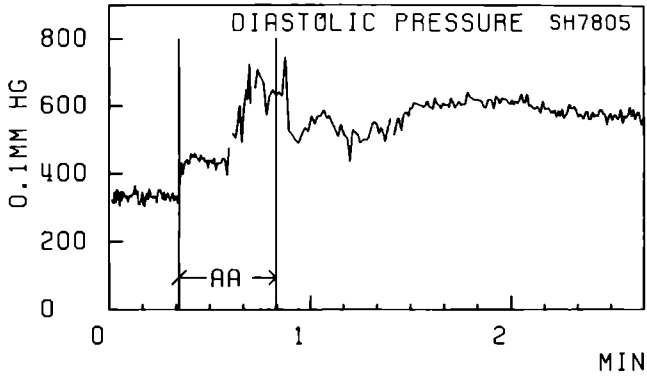


Figure 5.3: Experiment no. SH 7805: diastolic blood pressure.

Figure 5.3 gives an example of the rise in diastolic blood pressure during an AA-occlusion. This recording, obtained during the same experiment as shown in figure 5.2 (SH 7805), illustrates the fetal arterial diastolic blood pressure to follow closely the pattern of change observed in the systolic pressure tracing: both the first and the second step increases can also be found in the diastolic pressure tracings.
The change in R-R interval is shown in figure 5.4.

Two steps can also be discerned in the change of the R-R interval during this occlusion, although not as clearly as in the arterial pressure recordings. In this experiment no recovery of the fetal heart rate (the reciprocal value of the R-R interval) could be observed during the 30 second occlusion period.

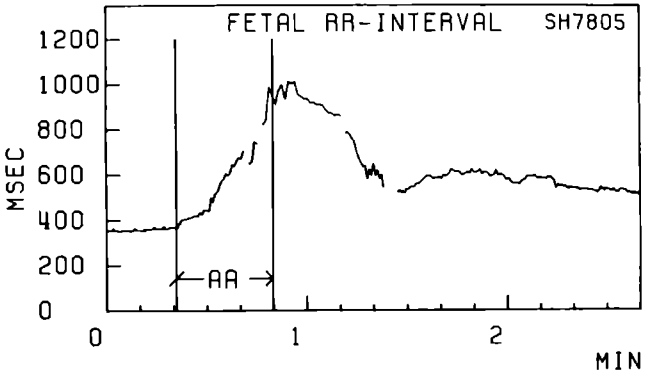


Figure 5.4: Experiment no. SH 7805: fetal R-R interval.

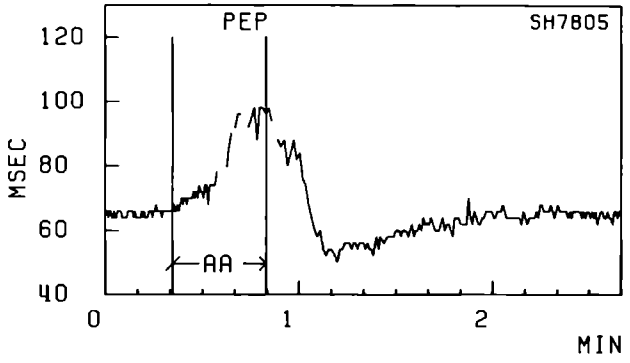


Figure 5.5: Experiment no. SH 7805: PEP (relative values only; cf conditions in chapter 4).

The fetal R-R interval did not show a consistent pattern of change during the second half of the occlusion.
A further increase of the R-R interval could be found, as

well as partial recovery towards the steady state level or a scale of rhythm disturbances (see section 5.2.2.1.4).

The patterns of change of the PEP were uniform and closely reflected those observed in the fetal arterial blood pressure tracings. Immediately following the onset of the AA-occlusions, a prolongation of the PEP occurred which was less abrupt than that observed in the corresponding pressure tracings. The second step increase observed in the blood pressure recordings was also very prominent in the PEP-tracings. Figure 5.5 shows the results calculated for the changes in the duration of the PEP during experiment SH 7805. The corresponding pressure tracings are shown in figures 5.2 and 5.3.

In each of the 13 AA occlusion experiments, an increase was seen in the duration of the PEP. This increase either reached a level which was present until the end of the occlusion period or was followed by the second step increase mentioned earlier. Prolongation of the PEP was found during the complete period of AA-occlusion in each of the experiments in lambs with an intact autonomic nervous system.

5.2.2.1.2 Occlusion of both umbilical veins

In contrast to the occlusions of the umbilical arteries, during the occlusions of the umbilical veins (code: VV), a certain time delay was found between the onset of the occlusion and the first changes in the cardiovascular parameters (fig.5.6). The increase in the fetal arterial blood pressure was less steep, and the onset of bradycardia less abrupt, than those occurring with AA occlusions. The secondary changes of blood pressure and heart rate, described earlier, are absent in the recordings of this particular experiment, although they were present in some of the VV occlusions.

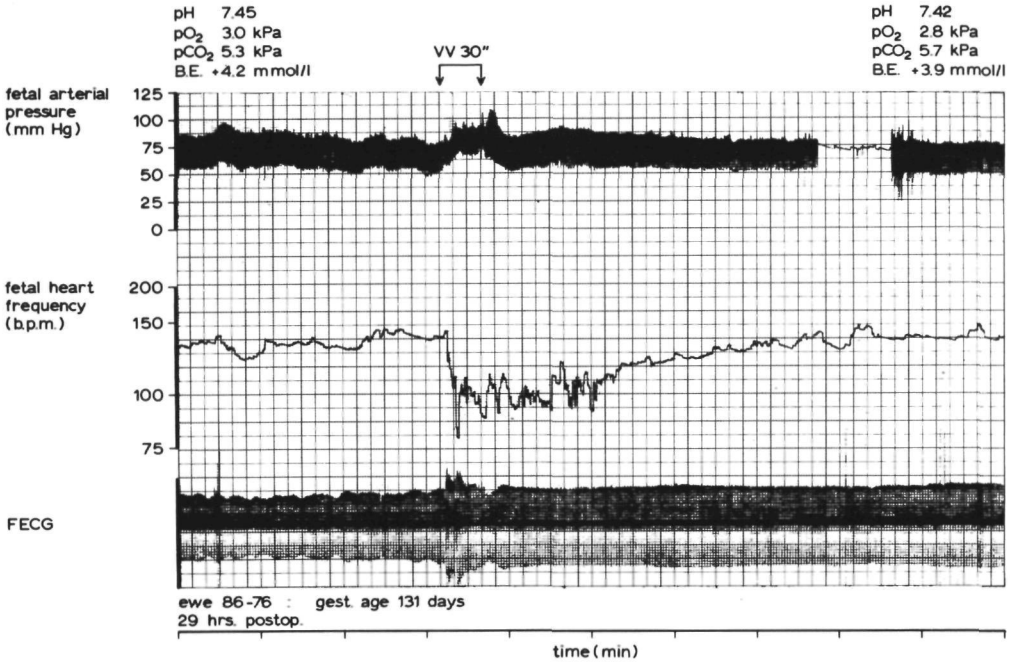


Figure 5.6: Occlusion of both umbilical veins (VV) for 30 seconds (30") in the fetal lamb of ewe 86-76. Results of blood sample analyses 5 minutes before and 5 minutes after the occlusion are indicated at the top of the figure.

A more detailed study of the pressure tracings obtained in the 20 VV occlusions shows that, in contrast to the steep increase in blood pressure immediately following the onset of the AA occlusions, an initial lowering of the fetal arterial blood pressure occurred consistently during the occlusions of the umbilical veins. This is particularly pronounced in the systolic pressure tracing (fig. 5.7).
Also during VV occlusions a second step increase in the fetal arterial blood pressure might be observed, most clearly in the diastolic pressure.

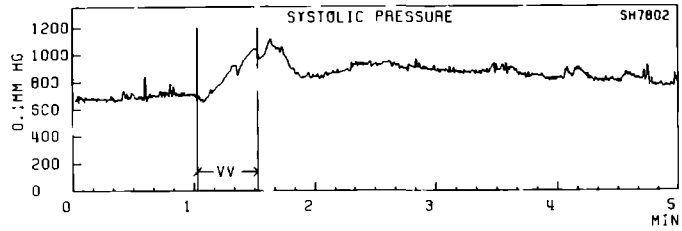


Figure 5.7: Occlusion of both umbilical veins (VV) indicated by the two vertical bars; experiment no. 2 in the fetal lamb of ewe 78-75.

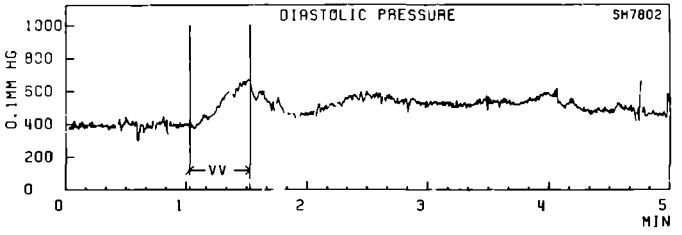


Figure 5.8: Experiment no. SH 7802: diastolic blood pressure.

The initial transient fall in fetal arterial systolic and diastolic blood pressures was always followed by an increase in both parameters above the pre-occlusion levels, which lasted until the end of the occlusion.

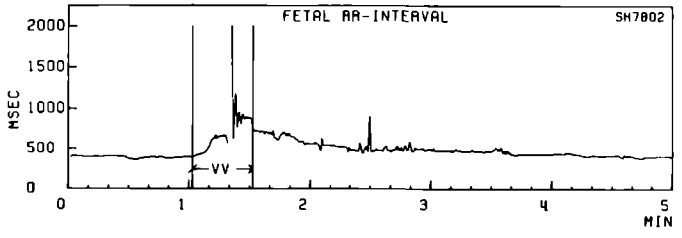


Figure 5.9: Experiment no. SH 7802: fetal R-R interval.

After an initial delay of 3 to 5 seconds immediately following the onset of the occlusion of both umbilical veins, the fetal

R-R interval started to increase (fig. 5.6; 5.9).
Rhythm disturbances were frequently observed during the second half of the occlusion, more frequently in poorly oxygenated fetal lambs (see chapter 5.2.2.1.4).
No initial delay could be detected during the VV occlusions in the reaction of the PEP.

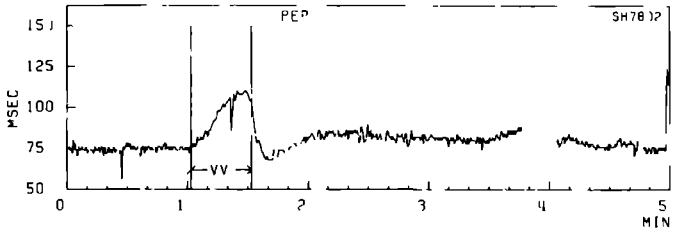


Figure 5.10: Experiment no. SH 7802: PEP

A slow but steady increase in the PEP began immediately following the onset of the occlusion.
If a second step increase in fetal arterial blood pressure was present, a second PEP increase occurred simultaneously.

The PEP became prolonged in each of the 20 VV occlusion experiments. This prolongation either was present until the end of the occlusion, or was followed by the second step increase described above.

5.2.2.1.3 Occlusion of the total umbilical cord

The changes in cardiovascular parameters induced by the simultaneous occlusion of both umbilical arteries and both umbilical veins referred to as total umbilical cord occlusion (code: TT), resembled those observed during AA occlusions.

An example of the cardiovascular changes in a total umbilical cord occlusion is shown in fig. 5.11.

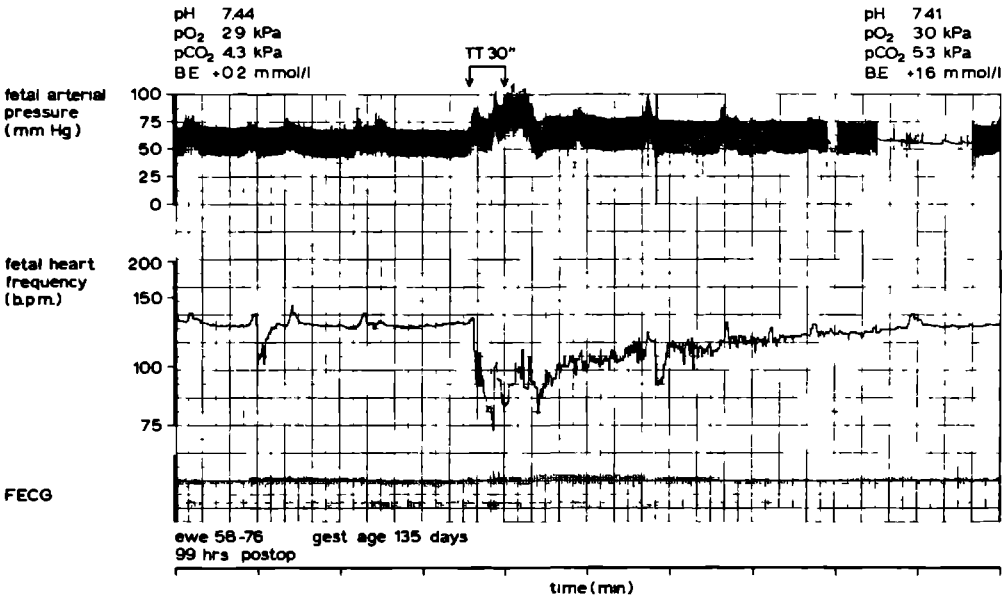


Figure 5.11: Occlusion of the total umbilical cord (TT) for 30 seconds (30") in the fetal lamb of ewe 58-76. Results of blood sample analyses 5 minutes before and 5 minutes after the occlusion are indicated at the top of the figure.

In all total umbilical cord occlusions, a rise in fetal systolic and diastolic arterial blood pressure was observed immediately following the onset of the occlusion, simultaneous with a sudden increase of the fetal R-R interval and a prolongation of the PEP.
Figures 5.12, 5.13, 5.14 and 5.15 show the reactions of the individual cardiovascular parameters during the TT occlusion in fetal lamb SH 7804.

The changes in fetal systolic (fig. 5.12) and diastolic blood pressure (fig. 5.13), R-R interval (fig. 5.14) and PEP (fig. 5.15) are comparable to those found in the AA occlusions.

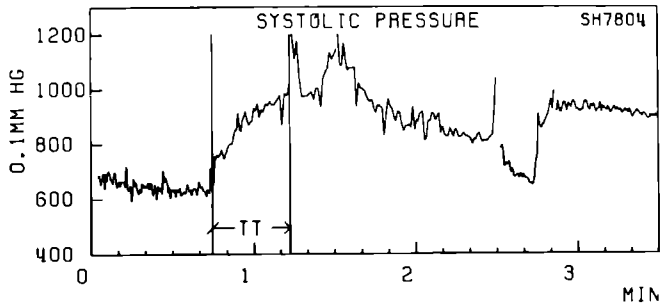


Figure 5.12: Occlusion of the total umbilical cord (TT) indicated by the two vertical bars; experiment no. 4 in the fetal lamb of ewe 78-75.

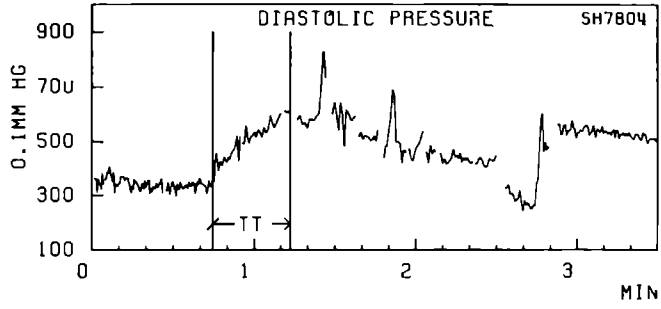


Figure 5.13: Experiment no. SH 7804: diastolic blood pressure.

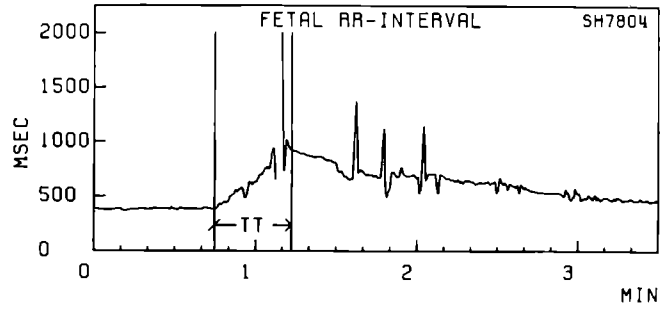


Figure 5.14: Experiment no. SH 7804: fetal R-R interval.

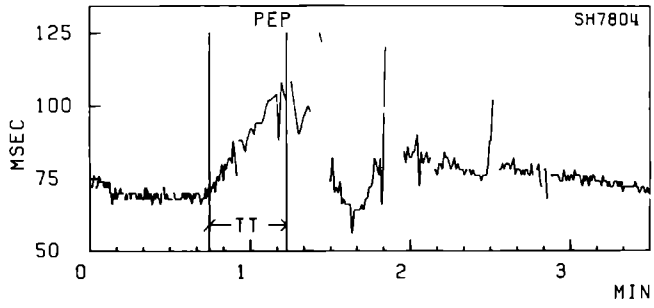


Figure 5.15: Experiment no. SH 7804: PEP.

An impression of the difference in the initial changes in blood pressure and PEP during the various types of occlusion can be gathered when the percentual changes in the first 10 AA, 10 VV and 10 TT occlusions are averaged.
As can be seen in fig. 5.16, there is an instantaneous increase in the systolic blood pressure immediately following the onset of the AA and TT occlusions. In the occlusions of both umbilical veins, however, the increase in systolic blood pressure is more gradual and is preceded by an initial transient decrease lasting 5 seconds.
No such difference could be observed in the response of the PEP to the various types of occlusion. As observed in the individual tracings also, the PEP started to increase immediately following the onset of every type of umbilical cord occlusion.
Statistical analysis of the results obtained in all occlusions in fetal lambs with an intact autonomic nervous system emphasized the difference in cardiovascular reaction to the occlusion of both umbilical veins on one hand and to the occlusion of both umbilical arteries or the complete umbilical cord on the other.
Comparison of the changes in fetal arterial systolic and diastolic blood pressure, R-R interval and PEP during the first 7.5 seconds of occlusion gave evidence of a highly significant positive difference between AA + TT occlusions and VV occlusions, regarding the systolic blood pressure ($p = 0.0006$),

the diastolic blood pressure (p = 0.0041) and the R-R interval (p = 0.0009).

Wilcoxon's two sample test was employed (Appendix I).

No such difference could be demonstrated with regard to the initial response of the PEP to the various types of occlusion (p = 0.97; Wilcoxon's two sample test).

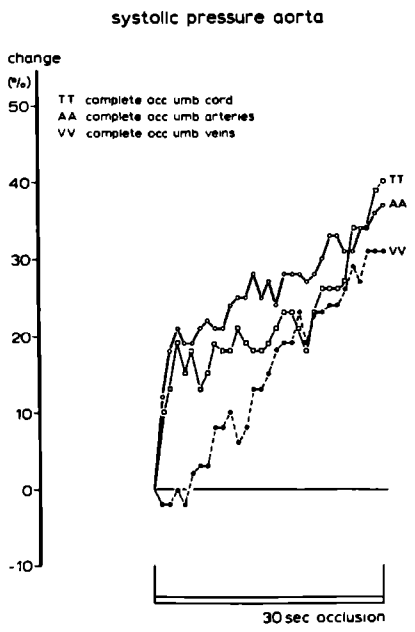


Figure 5.16:
Cumulative plot of the averaged values of the systolic blood pressure during the 30 seconds of occlusion in 10 AA, 10 VV and 10 TT-experiments. Percent change is indicated on the ordinate; duration of the occlusion on the abscissa.

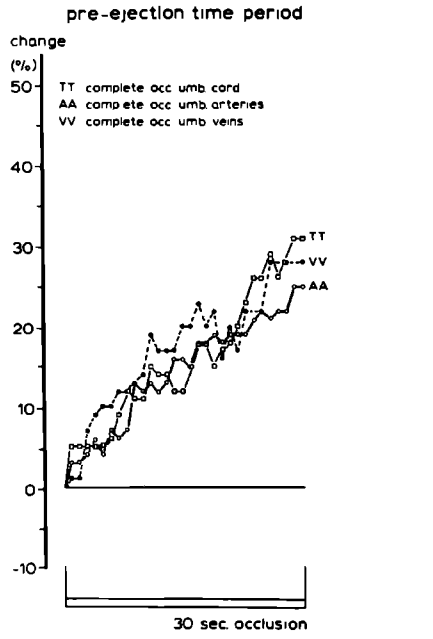


Figure 5.17:
Cumulative plot of the averaged values of the PEP during the 30 seconds of occlusion in 10 AA, 10 VV and 10 TT-experiments. Percent change is indicated on the ordinate; duration of the occlusion on the abscissa.

5.2.2.1.4 Fetal oxygenation and response to the occlusion

The response of the fetal arterial systolic and diastolic blood pressures to the occlusion consisted of an increase, either immediate and steep in case of an occlusion of the umbilical arteries and of the complete umbilical cord, or slightly delayed and more gradual and preceded by an initial decrease in case of occlusion of the umbilical veins.
The levels of blood pressure reached after this first rise was between 10 and 20 mmHg over the pre-occlusion values for systolic blood pressure and between 5 and 15 mmHg for diastolic blood pressure.

In some of the occlusion experiments, a second increase in blood pressure was seen consisting of an additional 10 to 20 mmHg increase in systolic pressure and 10 to 25 mmHg further elevation of diastolic pressure. Whenever this second blood pressure rise occurred, a comparable secondary prolongation of the PEP was observed.
The PEP, after lengthening by between 5 and 20 milliseconds in the first part of the occlusion, now showed a further prolongation of 10 to 20 milliseconds.

It is difficult to objectify the significance of the second step in blood pressure and PEP rise during the occlusion, since the identification of such a second step increase is based chiefly upon visual pattern recognition. If, however, the second step increase in the prolongation of the PEP is defined as a secondary lengthening of the PEP during the 30 seconds' occlusion which at least is equal to the amount of increase immediately following the occlusion, and which is separated from this initial increase by a (short) period of constant PEP values, 9 of the 46 occlusion experiments (in fetal lambs with intact autonomic nervous systems) demonstrated such a second step increase in the prolongation of the PEP (group A). The steady state values of the PO_2 in these expe-

riments ranged from 0.1 to 2.2 kPa, with one exception (2.6 kPa).
A second category of experiments was formed, consisting of those registrations in which the second step increase was definitely absent (group B). This category consisted of 15 occlusions. The steady state values of PO_2 in these experiments ranged from 2.4 to 4.5 kPa, also with one exception (2.1 kPa).
The remaining group was formed by those recordings in which the presence or absence of a second step increase in the PEP could not be ascertained unequivocally. This last category was composed of 22 recordings in which the possible second step increase either was too small or its angle of inclination too faint to allow an identification of this second step as a separate entity within the pattern of PEP changes during the occlusion (group C). PO_2 : 1.8 - 4.0 kPa.
No apparent differences between the various categories of PEP responses could be noted in the results of pH and PCO_2 determinations during the steady state preceding the occlusion. In contrast, 8 of the 9 steady state PO_2 values in group A (second step increase present) were 2.2 kPa or less, whereas 14 out of 15 PO_2 values in group B (second step increase absent) were 2.4 kPa or more.
Taking into account a possible bias in the way of identifying the second step increase in the PEP, these figures are suggestive for a relation between the occurrence of a second step increase in the prolongation of the PEP during the occlusion and the state of fetal oxygenation at the moment of cord occlusion.

Changes in the R-R interval during the 30 seconds of occlusion were less abrupt. A second step sometimes could be recognized in the R-R interval recording. On other occasions however a shortening of the R-R interval could be observed even before the end of the occlusion (fig. 5.3).
Serious rhythm disturbances were found to interfere with the

heart rate pattern recording in poorly oxygenated fetal lambs.

In general, the R-R interval recordings, and hence heart rate patterns, often revealed rhythm disturbances during the second half of the occlusion, especially when the steady state PO_2 and pH prior to the occlusion were low.
The arrhythmias that were observed varied from first and second degree atrioventricular conduction defects to complete heart block (fig. 5.18 a-e).

Atropine prevented the occurrence of myocardial conduction defects in all occlusions lasting 30 seconds, propranolol enhanced the appearance of arrhythmias during the period of cord occlusion (chapter 5.2.2.2).

No correlation was found between the degree of prolongation of the PEP during the occlusion (AA + VV + TT) and the initial steady state PO_2 ($p = 0.63$; Spearman's test for rank correlation), nor between the prolongation of the R-R interval and the control PO_2 ($p = 0.37$; Spearman's test)(Appendix I).
A weak correlation appeared to exist between the rise in fetal arterial systolic blood pressure during the occlusion and the control PO_2 ($p = 0.0536$; Spearman's test), whereas the rise in fetal arterial diastolic blood pressure during the occlusion correlated significantly with the control PO_2 ($p = 0.003$; Spearman's test).
No relation could be established between either of the four cardiovascular parameters and the initial steady state control values of pH ($p > 0.05$; Spearman's test).
The change in the cardiovascular parameters during the occlusion was calculated as the difference between their respective median values during the final 7.5 seconds of occlusion and the median value during the steady state before occlusion.

Figure 5.18 (next page): Progressive increase of atrioventricular conduction defect during 30 seconds of simultaneous occlusion of both umbilical veins in the fetal lamb of ewe 69-75. Period of occlusion indicated by arrows.

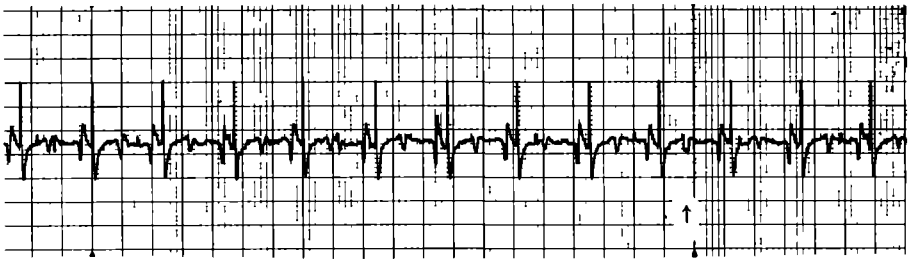


Figure 5.18 a

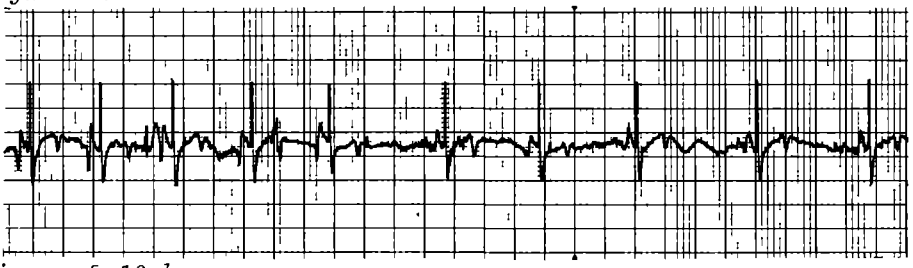


Figure 5.18 b

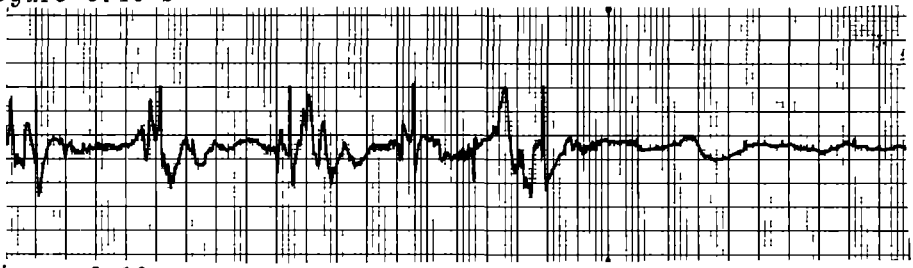


Figure 5.18 c

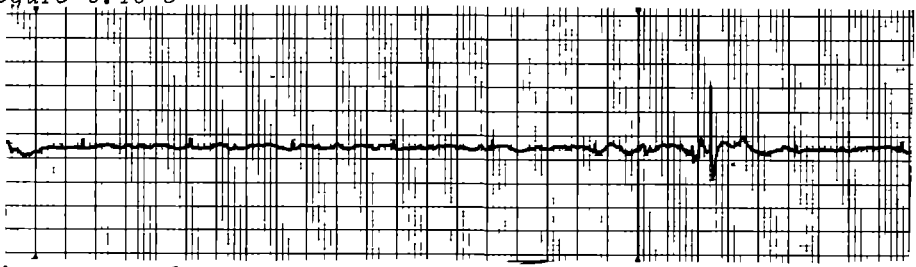


Figure 5.18 d

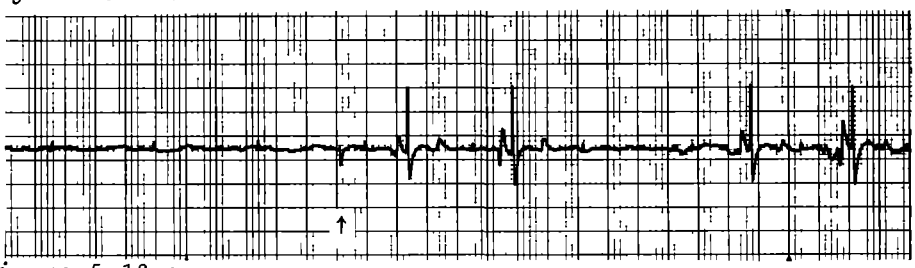


Figure 5.18 e

5.2.2.1.5 Summary of observations

- During occlusions of both umbilical arteries, of both umbilical veins, as well as during occlusions of the complete umbilical cord, a consistent rise in blood pressure and PEP was seen, which was present till the end of the occlusion.
- During occlusions of both umbilical veins the increase in blood pressure was preceded by an initial decrease lasting 3-5 seconds, which was most distinct in the systolic blood pressure tracing.
- No such initial decrease could be found in the duration of the PEP during occlusions of the umbilical veins. This parameter showed a gradual but steady prolongation directly from the start of the occlusion of the umbilical veins as well as of the umbilical arteries and of the complete umbilical cord.
- A highly significant difference was noted in the initial response of the fetal systolic and diastolic blood pressures and of the fetal R-R interval between occlusions of both umbilical veins on one side and occlusions of both umbilical arteries or the complete cord on the other ($p = 0.0006$; $p = 0.0041$ and $p = 0.0008$, respectively; Wilcoxon's two sample test). No such difference was observed in the pattern of PEP change ($p = 0.97$; Wilcoxon's test).
- No decrease in systolic or diastolic blood pressure, nor in the PEP was observed during the period of occlusion (30 seconds), when the autonomic nervous system was left intact, apart from the initial pressure dip in VV occlusions.
- In some of the experiments, a second step increase in PEP during the occlusion could be observed. The occurrence of this second step was suggested to be related to the PO_2 in the steady state sample prior to the occlusion.
- Whenever this second step increase in PEP occurred it was accompanied by a second step increase in the fetal arterial blood pressure. This was most pronounced in the diastolic pressure tracing.

- A less obvious second step could sometimes be observed in the R-R interval change during the occlusion.
- In some experiments the fetal heart rate began to recover already during the occlusion to a less extreme level of bradycardia. When this occurred the fetal arterial blood pressure increased still further.
- Rhythm disturbances of the fetal heart action occurred during the occlusion, especially in poorly oxygenated fetal lambs. These consisted of conduction defects, particularly increasing degrees of AV-block.

5.2.2.2 Blockade of parts of the autonomic nervous system

The role of the autonomic nervous system in the cardiovascular responses during the various types of cord occlusion was studied by blocking parts of this system pharmacologically. A total of 38 umbilical cord occlusions has been performed in 6 different fetal lambs after the administration of the various autonomic blocking agents (table 5.7).

blocking agent	number of occlusions			number of fetal lambs
	umbilical veins	umbilical arteries	total cord	
atropine	8	6	5	5
phentolamine	4	4	3	1
propranolol	3	3	2	1

Table 5.7: Occlusions with a selective blockade of the autonomic nervous system, arranged according to the type of occlusion performed and the blocking agent employed.

5.2.2.2.1 Cholinergic blockade

No significant difference could be observed in the pattern of the fetal systolic and diastolic arterial blood pressures during the occlusions with atropine blockade of the cholinergic system, as compared to the results from experiments with an intact autonomic nervous system.

Both steps of blood pressure rise observed during the various umbilical cord occlusions described earlier (section 5.2.2.1.4) also occurred during occlusions after cholinergic blockade (fig. 5.19 and 5.20).

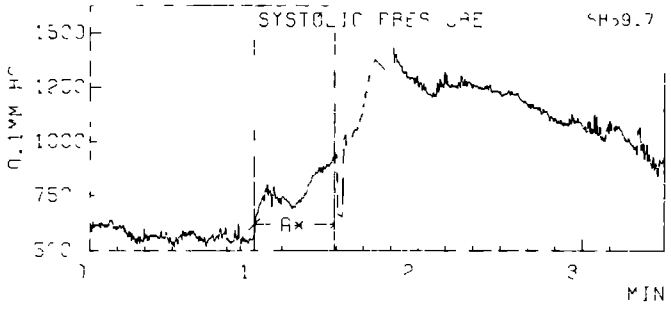


Figure 5.19: Occlusion of both umbilical arteries indicated by the two vertical bars, after the administration of atropine (Ax); experiment no. 17 in the fetal lamb of ewe 69-75.

No difference of statistical significance was noted in the increase in systolic and diastolic blood pressure during the occlusion, compared to the non-blocked situation ($p = 0.52$ and $p = 0.20$, respectively; Wilcoxon's two sample test).

The initial fall in fetal arterial systolic blood pressure immediately following the onset of the occlusion of the umbilical veins was also found during cholinergic blockade (fig. 5.21).

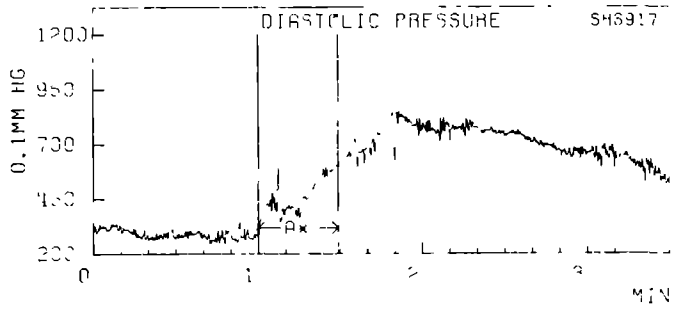


Figure 5.20: Experiment no. SH 6917: diastolic blood pressure.

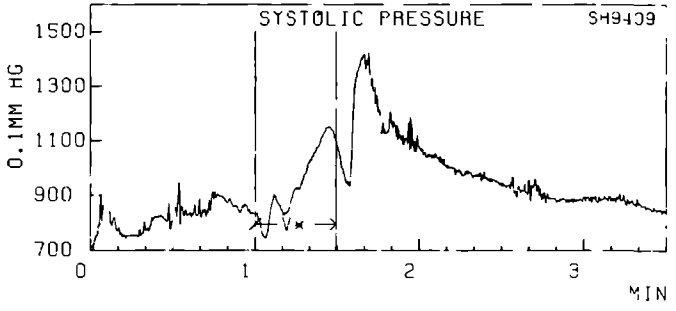


Figure 5.21: Occlusion of both umbilical veins indicated by the two vertical bars after the administration of atropine (V✱); experiment no. 9 in the fetal lamb of ewe 94-75.

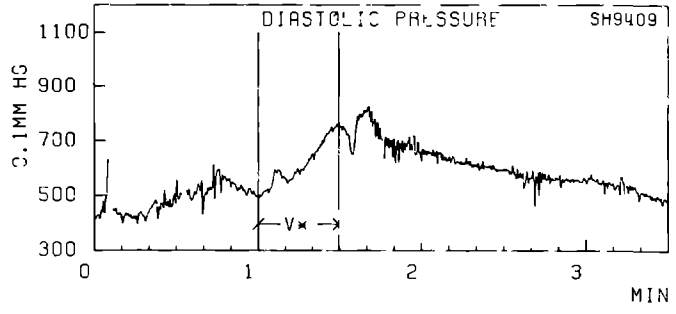


Figure 5.22: Experiment no. SH 9409: diastolic blood pressure.

Also in the occlusions during cholinergic blockade, a second PEP rise occurred (fig. 5.23),simultaneously with the second pressure rise. Four of the 23 occlusions exhibited such a second step. Their steady state PO_2's ranged from 1.1 to 2.2 kPa, whereas the PO_2's in the remaining experiments, none of which showed a distinct second step increase, were 2.2 kPa or greater.

The increase in PEP during occlusions with cholinergic blockade ranged from 5 to 30 msec. No difference of statistical significance was observed comparing this increase with the prolongation of the PEP during cord occlusions (AA + VV + TT) in fetal lambs with intact autonomic nervous systems ($p = 0.36$; Wilcoxon's two sample test).

In contrast to these findings the reaction of the fetal heart rate to occlusion of the umbilical circulation during cholinergic blockade was quite different from that during occlusions with an intact autonomic nervous system.

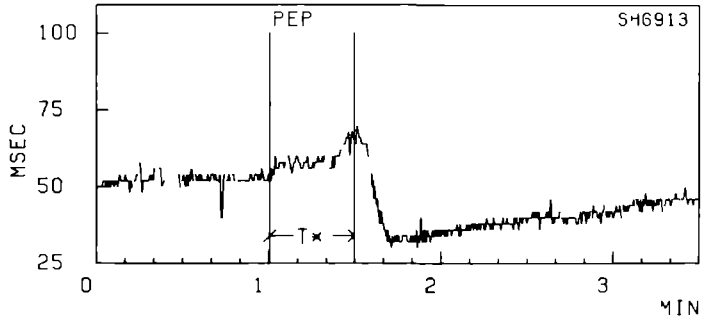


Figure 5.23: Occlusion of the total umbilical cord indicated by the two vertical bars, after the administration of atropine (Tx); experiment no. 13 in the fetal lamb of ewe 69-75.

If defining a change in R-R interval as an increase or decrease greater than 75 msec, most often (11 of 19 experiments) the fetal R-R interval did not change during the period of occlusion (fig. 5.24), regardless of the kind of occlusion performed

(arterial, venous or total cord).
In figure 5.24 the reaction of the fetal R-R interval to the occlusion of the complete umbilical cord is shown in two consecutive experiments in the same fetal lamb (ewe 69-75); the first with intact autonomic nervous system (TT), and the second during blockade of the cholinergic division of the autonomic nervous system by means of atropine (code: T*). The results of the blood sample analyses prior to each occlusion were comparable on both occasions (table 5.8).

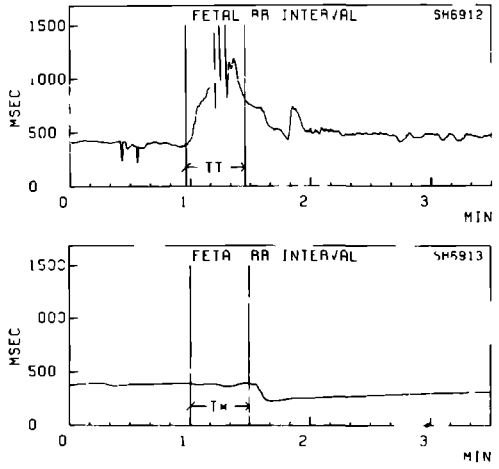


Figure 5.24:
Occlusion of the complete umbilical cord, indicated by the two vertical bars; experiment no. 12 and 13 in the fetal lamb of ewe 69-75, before (TT) and after administration of atropine (T).*

In order to facilitate assessment of the changes in fetal heart rate, the FHR is plotted in beats per minute in fig. 5.25.
Instead of the abrupt and profound bradycardia seen during the complete umbilical cord occlusion with an intact autonomic nervous system, no change in fetal heart rate was observed during the same type of occlusion after atropine.

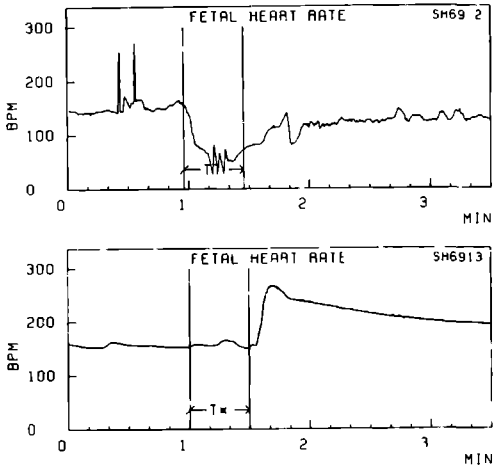


Figure 5.25:
Experiments no. SH 6912 and SH 6913.

	SH 6912	SH 6913	
pH	7.34	7.34	
PO_2	2.2	2.2	kPa
PCO_2	6.8	6.7	kPa
BE	+ 1.5	- 0.7	mmol/L

Table 5.8: Acid/base balance and blood gas values during the steady state prior to experiments no. 12 and 13 in the fetal lamb of ewe 69-75.

Other observations in fetal lambs with a blocked parasympathetic system included loss of short term irregularity and absence of rhythm disturbances during the occlusion.

Fig. 5.25 also shows that the baseline fetal heart rate was increased during cholinergic blockade. Sixty seconds of steady state registration with intact autonomic nervous system revealed a median value for the fetal heart rate of 145 beats per minute (upper panel), whereas the median FHR was 155 b.p.m. after atropine (lower panel).

In the remaining 11 cord occlusion experiments after atropine the R-R interval changed during cord occlusion; however, the pattern was not consistent. In six experiments an increase of the R-R interval was observed during the occlusion (fig. 5.26), indicating a fall in heart rate (fig. 5.27).
In two experiments the R-R interval decreased during cord occlusion (fig. 5.28), indicating a rise in fetal heart rate (fig. 5.29).

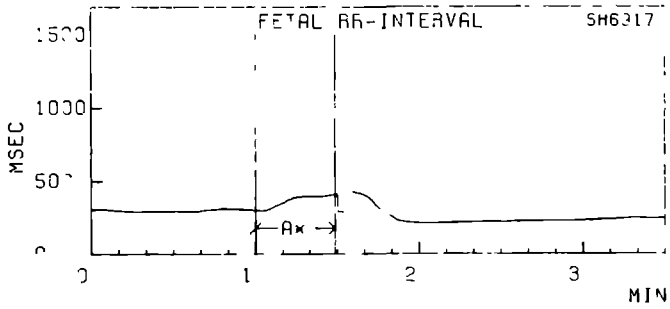


Figure 5.26: Occlusion of the umbilical arteries indicated by the two vertical bars, after the administration of atropine (Ax); experiment no. 17 in the fetal lamb of ewe 69-75.

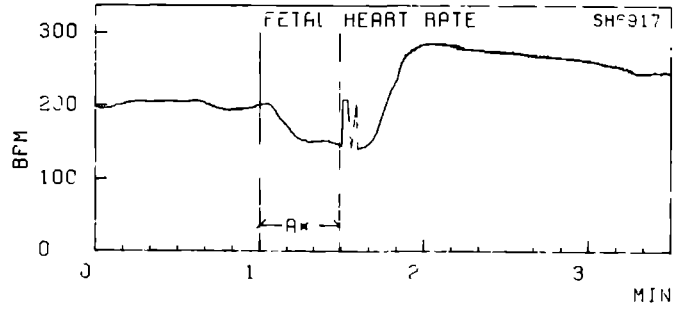


Figure 5.27: Experiment no. SH 6917: fetal heart rate.

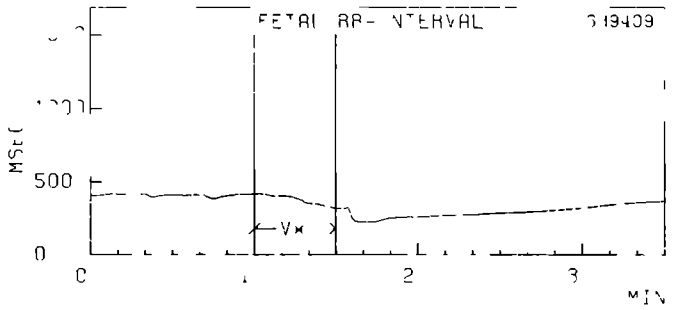


Figure 5.28: Occlusion of the umbilical veins indicated by the two vertical bars, after the administration of atropine (Vx); experiment no. 9 in the fetal lamb of ewe 94-75.

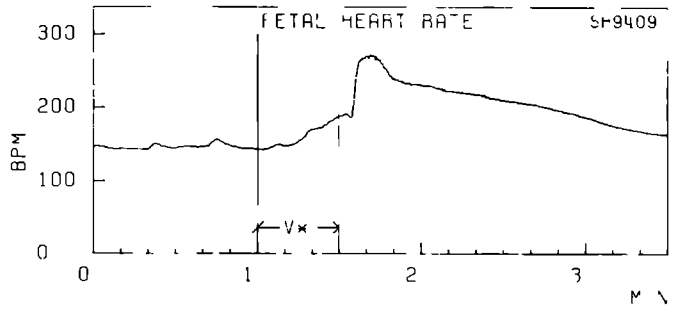


Figure 5.29: Experiment no. SH 9409: fetal heart rate.

In experiment 5605 the occlusion of both umbilical arteries could not be abolished because of a defect in the tubing connected with the inflatable balloon used to perform the occlusion.

Here, after some minor initial changes in the fetal R-R interval during the first 120 seconds of occlusion at a level comparable to the pre-occlusion values (420 msec), a second degree heart block developed, lasting exactly 60 seconds (fig. 5.34 and 5.31).

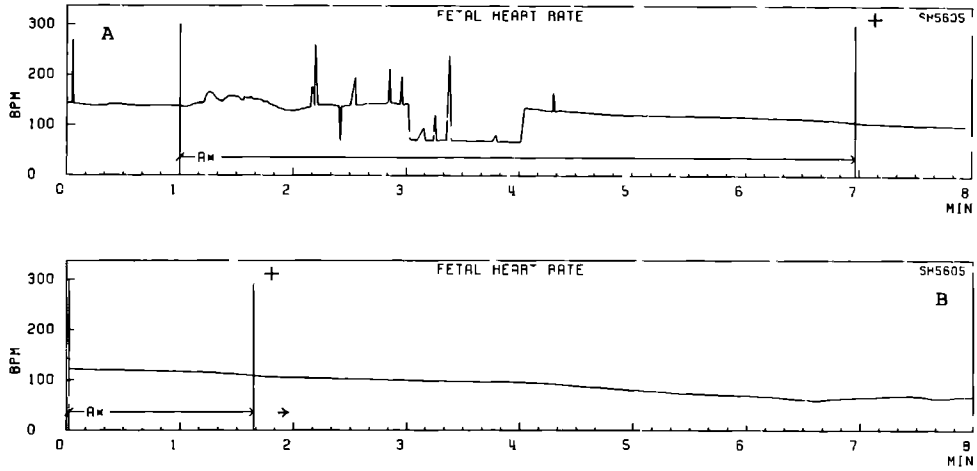


Figure 5.30: Occlusion of the umbilical arteries after the administration of atropine (Ax), experiment no. 5 in the fetal lamb of ewe 56-75. The occlusion could not be abolished. The first vertical bar indicates the start of the occlusion. The second vertical bar, marked with an asterix, indicates the same moment of the occlusion as does the vertical bar with asterix in the lower panel, which is the continuation of the first.

A = steady state sample before occlusion: pH 7.41; PO_2 2.1; PCO_2 6.5; BE + 6.1

B = sample after 12 minutes of occlusion: pH 7.03; PO_2 1.3; PCO_2 11.0; BE - 11.3

+ = indicating corresponding moment of occlusion in both tracings (not end of occlusion).

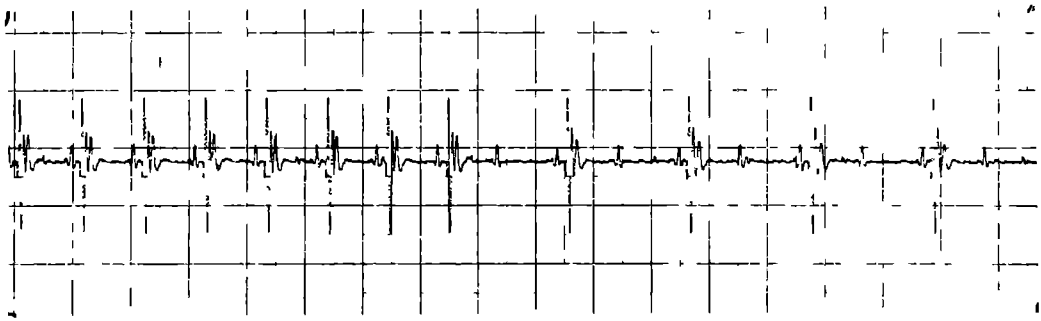


Figure 5.31: Change of a normal sinus rhythm into a 2:1 AV-block in the fetal lamb of ewe 56-75 during an irreversible occlusion of the umbilical arteries.

A slowly progressive bradycardia then followed from the 182nd second of occlusion till the end of electrical cardiac activity after about 30 minutes. It should be noted that, after about 10 minutes of occlusion and long before the fetal cardiac electric activity stopped, fetal arterial blood pressure had fallen to levels which indicated cessation of effective circulation.

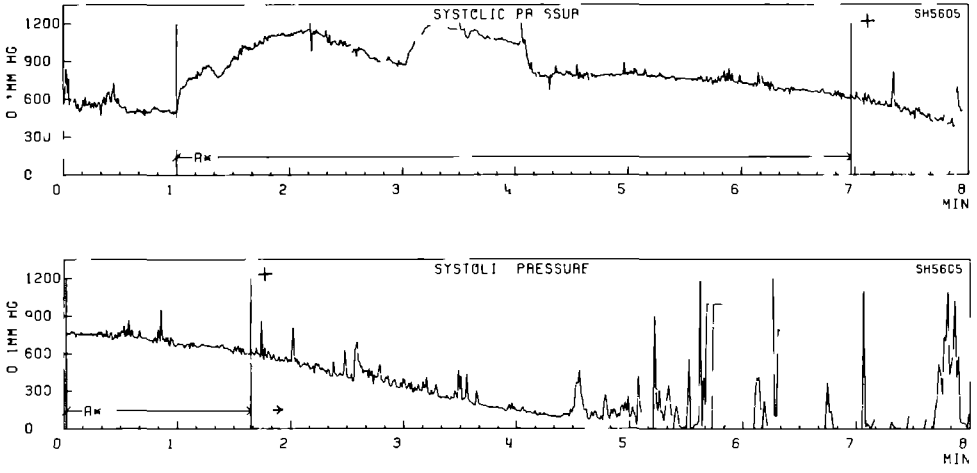


Figure 5.32: Experiment no. SH 5605: systolic blood pressure. Legends as in figure 5.30.

Some other interesting events can be observed in this recording of a fetal death in utero. First, fetal systolic and diastolic arterial blood pressures (fig. 5.32 and fig. 5.33), after rising instantaneously at the moment of occlusion and exhibiting a second step increase after about 20 seconds, continued to rise till about the 70th second of the occlusion. Then a slow decrease of fetal arterial blood pressure, both systolic and diastolic, was noted until the start of the second degree heart block at 122 seconds after the start of the occlusion. Simultaneously with the decrease in the fetal heart rate from 130 till 65 beats per minute (fig. 5.30), the arterial systolic blood pressure increased by about 30 mmHg, from 87 to 120 mmHg. The diastolic blood pressure did not increase but rather continued to decrease at its original rate.

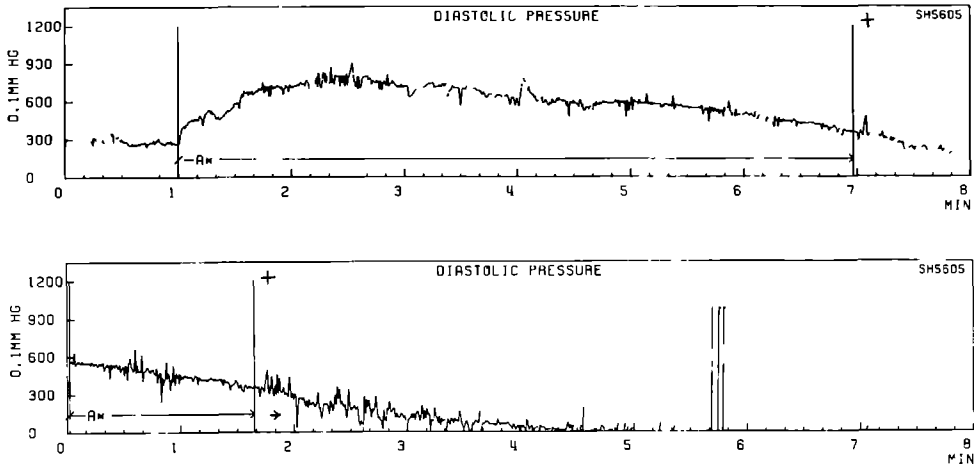


Figure 5.33: Experiment no. SH 5605: diastolic blood pressure (cf 5.30).

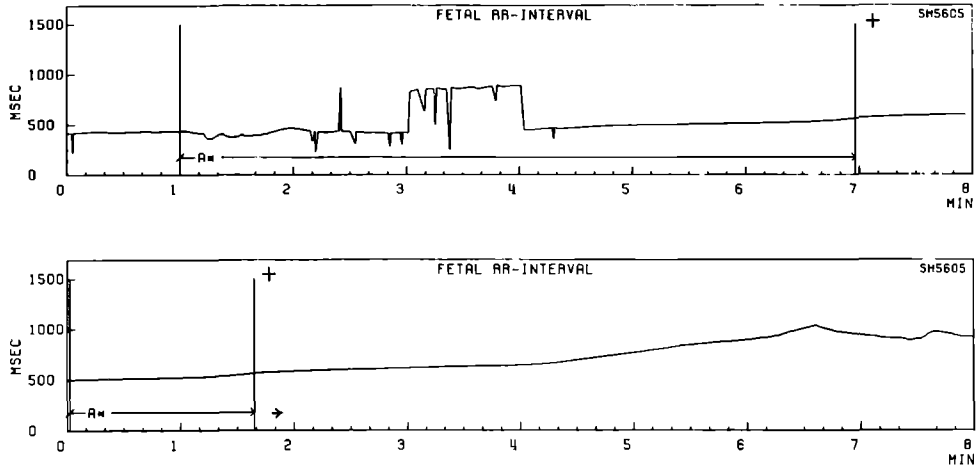


Figure 5.34: Experiment no. SH 5605: fetal R-R interval. Legends as in fig. 5.30.

At the end of the heart block, the systolic blood pressure returned to its previous level and continued to fall from that level. Both systolic and diastolic pressures reached pre-occlusion values (50 and 27 mmHg, respectively) simultaneously, 7 minutes after the start of occlusion.

The duration of the PEP increased immediately following the start of the occlusion. This increase persisted until the 50th second of occlusion, when a shortening of the PEP developed,

lasting 40 seconds. Subsequently, the PEP first increased again and then fell slowly until the pre-occlusion level was reached after 10 minutes of occlusion. Further measurement of the PEP was impossible due to the vanishing amplitude of the pressure signal. The second period of prolongation was interrupted for 60 seconds during the second degree heart block, when the PEP was shortened from 72 to 52 msec (fig. 5.35).

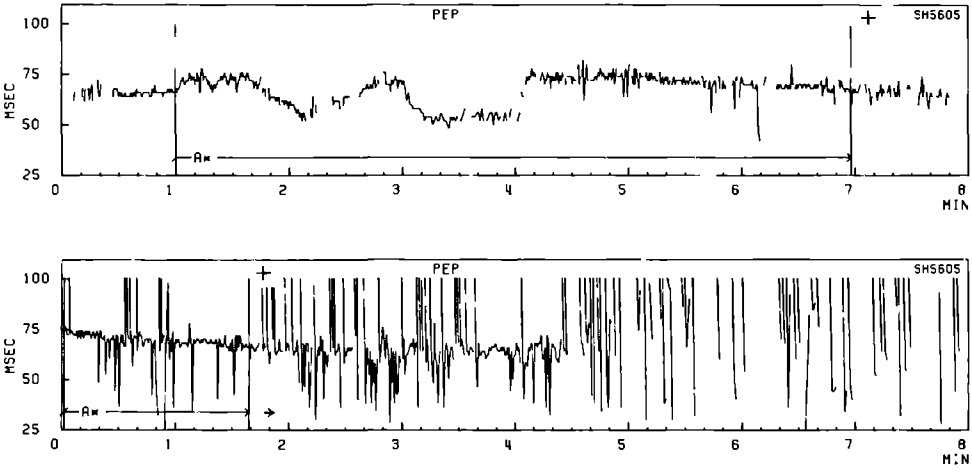


Figure 5.35: Experiment no. SH 5605: PEP. Legends as in fig. 5.30.

5.2.2.2.2 Alpha-adrenergic blockade

Blockade of the alpha-adrenergic component of the sympathetic nervous system by phentolamine, which prevents the stimulation of the alpha-receptors by nor-epinephrine and epinephrine, resulted in considerable changes in the cardiovascular reactions to occlusion of the umbilical circulation.
As in the control occlusions, the fetal arterial systolic and diastolic blood pressures first exhibited an increase during cord occlusions after phentolamine. The further pattern of blood pressure change differed, however, from that previously described for intact or atropine-blocked fetuses. No second step rise in systolic or diastolic blood pressure occurred during occlusions after alpha-adrenergic blockade.

Moreover, the increase in blood pressure during the first part of the occlusion did not persist throughout the complete period of occlusion. During the latter part of the occlusion period, both systolic and diastolic blood pressures declined to pre-occlusion levels or even below (fig. 5.36; 5.37; 5.38), with the diastolic blood pressure exhibiting the greatest fall.

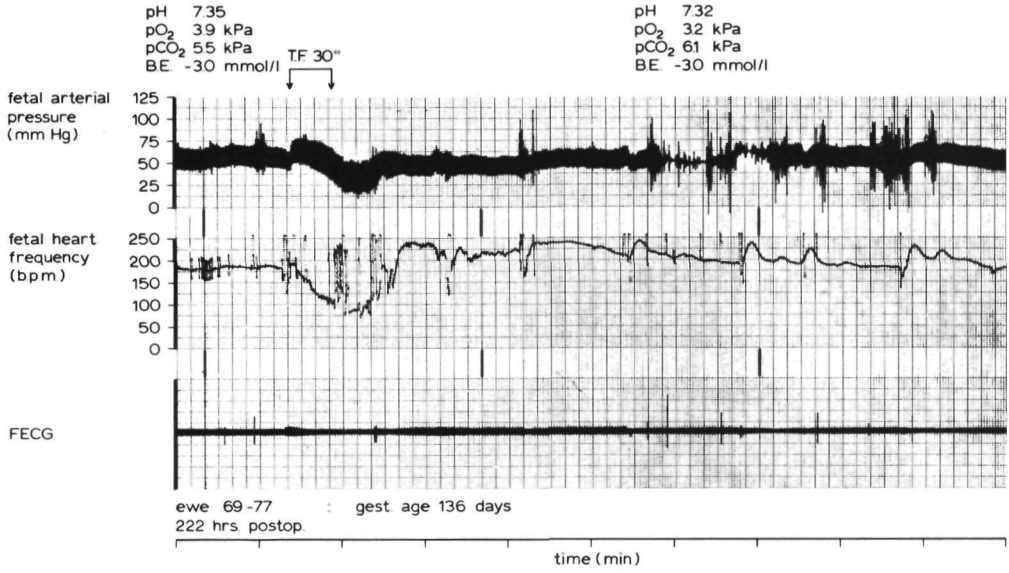


Figure 5.36: Occlusion of the complete umbilical cord (TF) during 30 seconds (30") in the fetal lamb of ewe 69-77, after the blockade of the alpha-adrenergic system by means of phentolamine. Results of blood sample analyses 5 minutes before and 5 minutes after the occlusion are indicated at the top of the figure.

In all three types of occlusion experiments (AF, VF and TF), bradycardia developed immediately following the onset of the occlusion (fig. 5.39).

The PEP also increased immediately following the onset of the occlusion in all three types of cord occlusions during alpha-

adrenergic blockade, but the increase did not persist until the end of the occlusion period. Instead, shortening of the PEP was observed during the second part of the occlusion (fig. 5.40), simultaneously with the fall in fetal diastolic blood pressure.

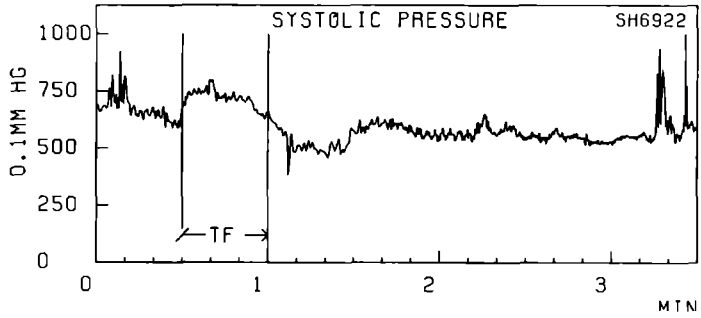


Figure 5.37: Occlusion of the total umbilical cord indicated by the two vertical bars, after the administration of phentolamine (TF); experiment no. 22 in the fetal lamb of ewe 69-77.

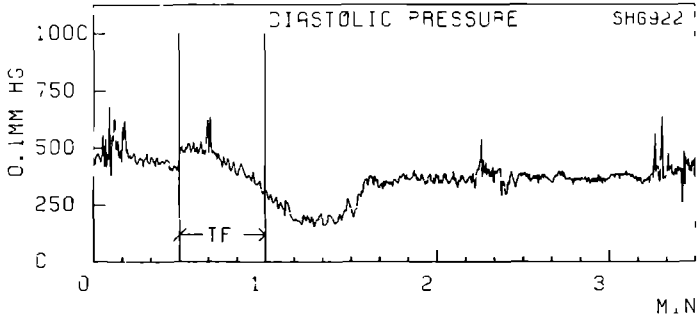


Figure 5.38: Experiment no. SH 6922: diastolic blood pressure.

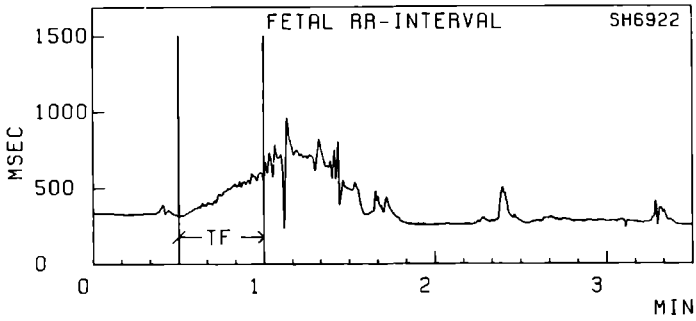


Figure 5.39: Experiment no. SH 6922: fetal R-R interval.

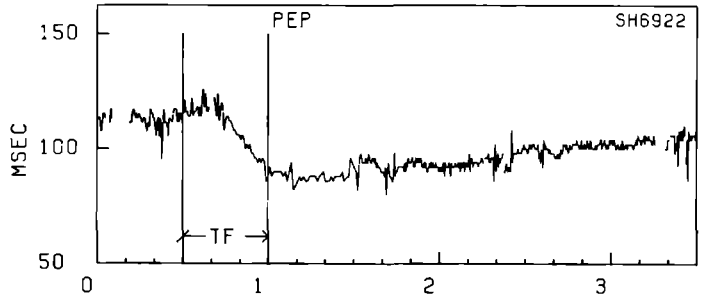


Figure 5.40: Experiment no. SH 6922: PEP.

5.2.2.2.3 Beta-adrenergic blockade

Blockade of the beta-adrenergic part of the autonomic nervous system by means of propranolol markedly altered the behavior of the fetal cardiovascular system during the occlusion of the umbilical circulation as compared to the non-blocked situation.

The most striking feature was the change in the fetal heart rate during occlusions under beta-adrenergic blockade. Bradycardia developed rapidly and evolved into serious rhythm disturbances resulting from conduction defects. Even asystole was observed in some of the experiments near the end of the occlusion period or shortly after release of the cord occlusion (fig. 5.41; 5.42; 5.43).

This exerted a profound influence upon the behavior of all the other cardiovascular parameters.

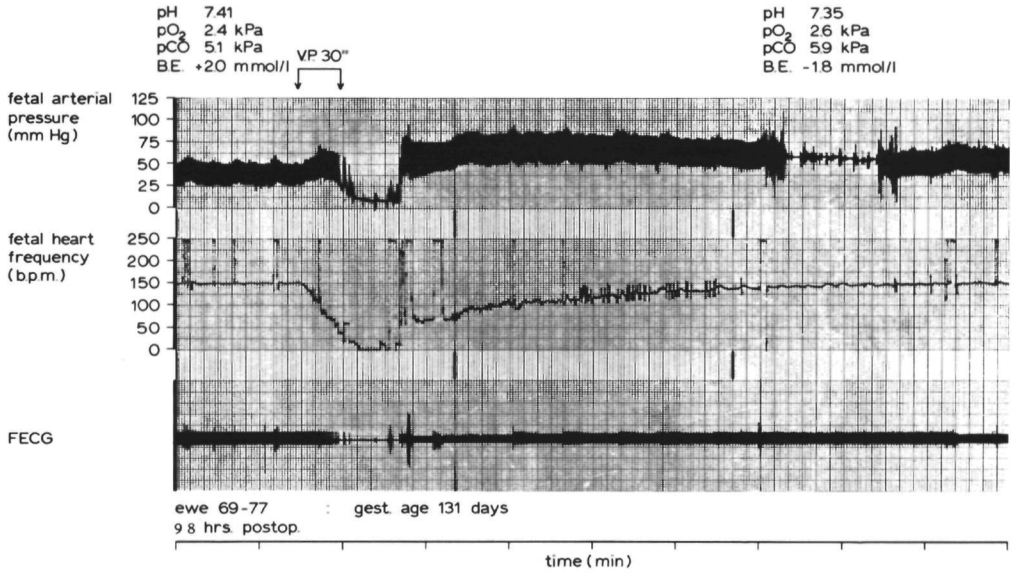


Figure 5.41: Occlusion of both umbilical veins (VP) during 30 seconds (30") in the fetal lamb of ewe 69-77, after the blockade of the beta-adrenergic system by means of propranolol. Results of blood sample analyses 5 minutes before and 5 minutes after the occlusion are indicated at the top of the figure.

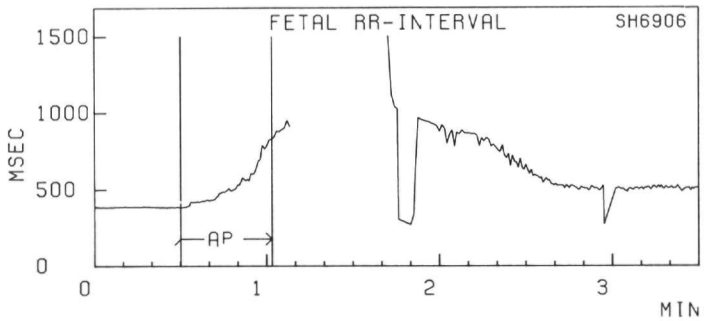


Figure 5.42: Occlusion of both umbilical arteries indicated by the two vertical bars, after the administration of propranolol (AP); experiment no. 6 in the fetal lamb of ewe 69-77.

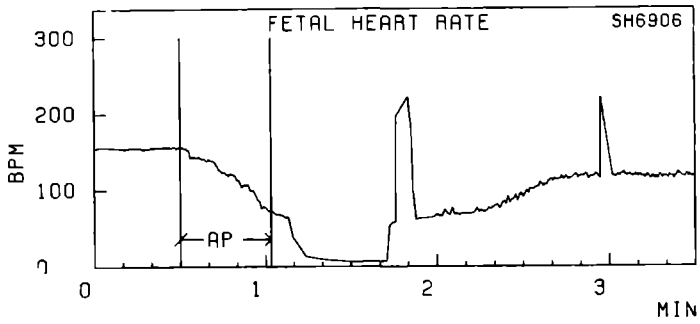


Figure 5.43: Experiment no. SH 6906: fetal heart rate

The fetal arterial systolic (fig. 5.44) and diastolic (fig. 5.45) blood pressures initially increased during (the first part of)the occlusion period, but collapsed when asystole occurred. This occurred with occlusions of the umbilical arteries, the complete umbilical cord, or the umbilical veins.

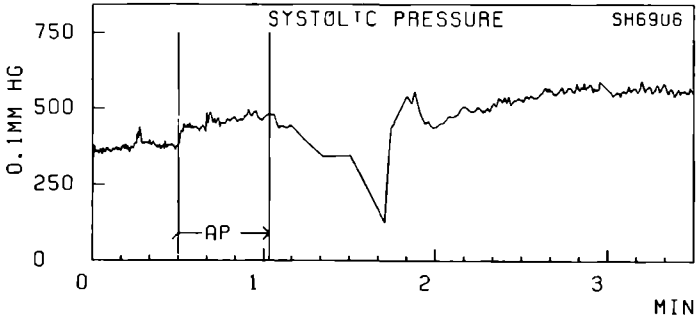


Figure 5.44: Experiment no. SH 6906: systolic blood pressure.

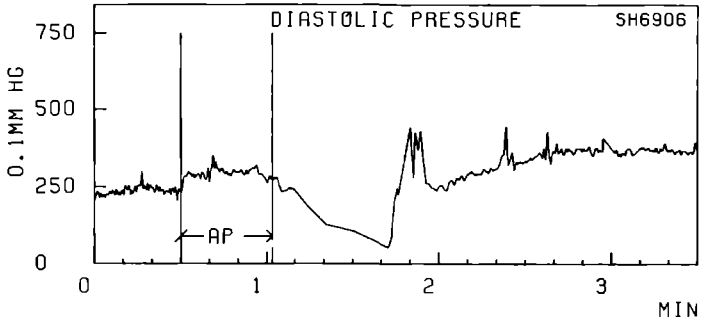


Figure 5.45: Experiment no. SH 6906: diastolic blood pressure.

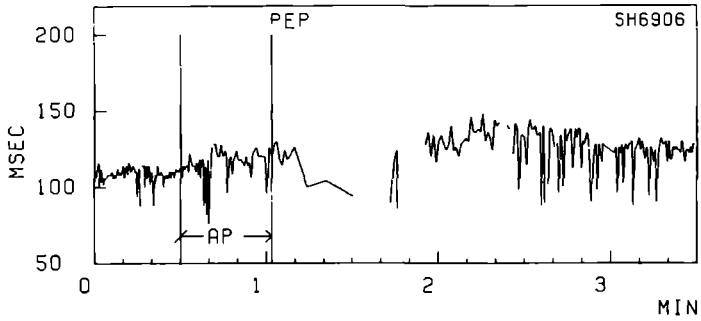


Figure 5.46: Experiment no. SH 6906: PEP

Once asystole occurred, the PEP could not, of course, be determined because of the absence of both the QRS-complex and the pressure pulse. In each occlusion experiment performed during the beta-adrenergic blockade the PEP was prolonged, throughout the period of the registration during which it could be determined (fig. 5.46).

5.2.2.2.4 Summary of observations

- During cholinergic blockade the changes in the fetal arterial systolic and diastolic blood pressures during the occlusion of the umbilical circulation showed no difference from the changes observed during occlusion experiments in lambs with an intact autonomic nervous system. Both the first and the second step increase in systolic and diastolic blood pressures were observed, and the degree of rise was comparable to that in the non-blocked situation ($p > 0.2$; Wilcoxon's two sample test). The initial lowering of the fetal arterial blood pressure, immediately following the onset of the occlusion of the umbilical veins,was observed also in venous occlusion experiments after the administration of atropine.
- The changes in the PEP during occlusions with cholinergic blockade were also comparable to those observed in fetal lambs with intact autonomic nervous systems. Both the first and the second steps in the prolongation of the PEP during the occlusion could be discerned.

The extent of prolongation of the PEP did not differ significantly from the one observed in the non-blocked condition ($p = 0.36$; Wilcoxon).

- With regard to the R-R interval, it was found that in about half of the experiments no significant change occurred during the occlusion of the umbilical circulation when the parasympathetic system was blocked. In some of the experiments a slight prolongation of the R-R interval was seen (equal to a fall in fetal heart rate) during the second half of the occlusion; while in others a shortening of the R-R interval was noted during the occlusion.
- A fetal death in utero, due to an irreversible occlusion of the umbilical arteries, demonstrated a slow fall in fetal heart rate (after an initial delay period with only minor heart rate changes), until fetal death occurred. A second degree atrioventricular conduction defect starting two minutes after the onset of the occlusion was accompanied by a shortening of the PEP, a rise in systolic arterial blood pressure, and no change in the diastolic pressure. This was the only time that a cardiac rhythm disturbance was seen in an atropinized fetus. After the end of the 2:1 block, systolic and diastolic blood pressures decreased further and finally the circulation stopped, although fetal cardiac electrical activity continued for 30 minutes.
  The duration of the PEP increased immediately following the onset of the occlusion and returned only gradually to the the pre-occlusion level again in the course of the first 10 minutes of occlusion. No shortening of the PEP below the control level was observed. After 50 seconds of occlusion a transient shortening of the PEP was seen, lasting 40 seconds. During a 2:1 AV-block, lasting 60 seconds, a decrease in PEP was found, together with the increase in fetal systolic blood pressure and the unaltered pattern of fall in the diastolic blood pressure.
- During alpha-adrenergic blockade, the occlusions of both veins or arteries or the complete umbilical cord caused an immediate rise in blood pressure. The elevated levels of

systolic and diastolic blood pressures were not maintained till the end of the occlusion. A decrease of fetal arterial blood pressure occurred during the latter part of the occlusion. The diastolic blood pressure decreased to values even below the initial steady state level. The duration of the PEP increased in all three types of occlusion experiments. The increase of the PEP did not persist till the end of the occlusion, and shortening was found during the second half of the occlusion together with the decrease in (especially the diastolic) blood pressure.
The fetal R-R interval always became prolonged during occlusions with alpha-adrenergic blockade, indicating a fall in heart rate.

- During beta-adrenergic blockade, a profound bradycardia was the main determining factor in all three types of occlusion experiments.
  The fact that this bradycardia rather quickly proceeded into a state of serious rhythm disturbances and asystole exerted a considerable influence upon the other cardiovascular parameters.
  After an initial rise, systolic and diastolic blood pressures collapsed when severe bradycardia or asystole developed.
  PEP was prolonged throughout the occlusion period, as long as effective electrical and mechanical cardiac activity was present.

5.2.2.3 Post-occlusion response

Following the release of the occlusion, all measured parameters returned to their initial steady state values. Some mechanisms influencing the post-occlusion recovery can be studied from the results of the individual measurements as described below.

5.2.2.3.1 Intact autonomic nervous system

Immediately following the end of the occlusion of the umbili-

cal arteries (fig. 5.1; 5.2; 5.3), veins (fig. 5.6; 5.7; 5.8), or of the complete umbilical cord (fig. 5.11; 5.12), a transitory dip was seen in the systolic and diastolic blood pressure tracings, lasting about 5-10 seconds.

After the short term hemodynamic disturbances, reflected in this post-occlusion blood pressure dip, an episode in the post-occlusion changes started which was initiated by shortening of the PEP.

The duration of the PEP decreased rapidly after the end of the occlusion to reach values below the pre-occlusion level in all of the experiments (fig. 5.5; 5.10; 5.15).

When the PEP reached its minimum, the fetal arterial blood pressure reached a new maximum which proceeded into a slow but gradual return towards the pre-occlusion level.

The fetal R-R interval returned slowly following the end of the occlusion (fig. 5.6; 5.11), and often the recording of the fetal heart rate at this moment was disturbed by cardiac arrhythmias. In some experiments, the recovery from the bradycardia exhibited a rapid initial phase evolving into a more slowly progressive return to normal levels described above. This rapid initial phase could be found to start even before the end of the occlusion (fig. 5.1).

In an attempt to objectify the relation between the state of fetal oxygenation at the moment of cord occlusion and the characteristics of the changes in cardiovascular parameters during the post-occlusion period, the median values of fetal systolic and diastolic blood pressures, R-R interval and PEP were calculated during a 7.5 sec period (between 22.5 and 30 seconds after the end of the occlusion) and compared to the pre-occlusion values. The relation between this difference and the steady state values of fetal pH and blood gases was studied.

No statistically significant relation could be found between either of the biochemical control values and the difference

between the post-occlusion value of the four cardiovascular parameters and their respective control values.
A weak negative relation ($\bar{r}_s$ = -0.383; p = 0.07; combined Spearman's test [appendix I]) was found, however, between the difference in R-R interval and the steady state pH, indicating a slower return of the bradycardia to normal, after the release of the cord clamping when the initial pH reflected a more serious degree of acidemia. A weak positive relation was found between the difference in PEP and the steady state pH ($\bar{r}_s$ = 0.428; p = 0.064; Spearman's test) as well as PO_2 ($\bar{r}_s$ = 0.447; p = 0.053; Spearman's test).
This suggests the post-occlusion PEP to be shorter compared with the steady state PEP when the state of fetal oxygenation at the moment of cord occlusion is worse. ($\bar{r}_s$ = mean value of Spearman's rank correlation coefficient).

5.2.2.3.2 Blockade of parts of the autonomic nervous system

5.2.2.3.2.1 Cholinergic blockade

During blockade of the parasympathetic division of the autonomic nervous system by means of atropine, no significant difference was seen in the behavior of the blood pressure, both systolic and diastolic, during the post-occlusion period as compared with the post-occlusion response in lambs with intact autonomic nervous systems (fig. 5.19; 5.20; 5.21; 5.22).
The duration of the PEP, however, remained shortened for a longer time after the release of the occlusion, returning to the initial steady state level very slowly.
Regardless of the state of fetal oxygenation, the duration of the PEP during the post-occlusion period was always shorter than the pre-occlusion values (cf fig. 5.23).
The fetal R-R interval, which in most of the experiments did not show considerable changes during the occlusion period, shortened immediately following the end of the occlusion, reflecting a marked degree of fetal tachycardia (200-300bpm). The R-R interval returned only slowly to its pre-occlusion level (fig. 5.24; 5.26; 5.28).

5.2.2.3.2.2 Alpha-adrenergic blockade

Fetal systolic and diastolic arterial blood pressures, which had decreased during the latter part of the period of cord occlusion after alpha-adrenergic blockade (fig. 5.37; 5.38), increased slowly to normal levels after the end of the occlusion . The fetal heart rate also recovered slowly and exhibited a late tachycardia (fig. 5.36), reflected in a shortened R-R interval (fig. 5.39).
The PEP, which had decreased during the occlusion, continued to be shortened in the post-occlusion period and only slowly returned to the pre-occlusion level (fig. 5.40).

5.2.2.3.2.3 Beta-adrenergic blockade

Fetal systolic and diastolic arterial blood pressures rose to levels clearly above those reached during the cord occlusion, provided that the post-occlusion rhythm disturbances did not interfere with the maintenance of fetal blood pressure (fig. 5.41; 5.44; 5.45).
Fetal heart rate patterns showed an extremely tardy recovery, with the rhythm disturbances occurring in the second half of the occlusion persisting into the early recovery phase (fig. 5.41; 5.42; 5.43).
The PEP increased to levels well above those measured during the cord occlusion (fig. 5.46), and returned slowly to the steady state level.

SUMMARY TABULATION I:

fetal cardiovascular parameter changes during umbilical cord occlusion and recovery.

BP = blood pressure
R-R = R-R interval
PEP = pre-ejection period
UCO = umbilical cord occlusion

A = atropine
F = phentolamine
P = propranolol
↗ = increase
↘ = decrease
~ = no change

UCO	early occlusion	late occlusion	early recovery	late recovery
BP	↗	↗ - ↗↗	↘ ↗	↘
R-R	↗	↗	↘	↘
PEP	↗	↗ - ↗↗	↘ - ↘↘	↗
UCO + A				
BP	↗	↗ - ↗↗	↘ ↗	↘
R-R	~	~	↘ ↘	↗
PEP	↗	↗ - ↗↗	↘ ↘	↗
UCO + F				
BP	↗	↘	↗	↗
R-R	↗	↗	↘	↘
PEP	↗	↘	↗	↗
UCO + P				
BP	↗	(↗)	(↘)	↘
R-R	↗	(↗)	(↘)	↘
PEP	↗	(↗)	(↘)	↘

5.3 Median uterine artery occlusions

In order to investigate the possibility of inducing fetal hypoxemia by obstructing the maternal side of the placental blood supply, occlusions of the median uterine arteries, either separately or in combination, were carried out in a series of 12 experiments.

5.3.1 Single median uterine artery occlusions

A total of 8 occlusions of one median uterine artery was performed in two fetal lambs.
The duration of occlusion was gradually increased in each succeeding experiment from 30 seconds to 60 minutes.
The results of the analyses of the blood samples obtained during the steady state prior to the occlusion, and after x minutes of occlusion are listed in table 5.9.
Although the uterine artery supplying the pregnant horn was occluded in each case, no remarkable change in acid/base balance and blood gases was produced by occlusion of this vessel.

5.3.2 Bilateral median uterine artery occlusions

A total of 4 simultaneous occlusions of both median uterine arteries was performed in three fetal lambs. The duration of the occlusions was gradually increased in each succeeding experiment from 15 to 60 minutes. The analyses of the blood samples obtained during the steady state prior to the occlusion, and after x minutes of occlusion are listed in table 5.10. In these experiments also no consistent change in the biochemical parameters was found, except for the PO_2.
The changes in this parameter were, however, not sufficient to allow a study of fetal cardiovascular responses to hypoxemia.

SH	BEFORE OCCLUSION				AFTER x MIN. OCCLUSION				
	pH	PO_2 (kPa)	PCO_2 (kPa)	BE (mmol/L)	pH	PO_2 (kPa)	PCO_2 (kPa)	BE (mmol/L)	x (min)
5503	7,38	2,9	5,9	+ 0,1	7,37	2,0	4,1	- 5,6	4
5504	7,40	3,4	3,8	+ 4,7	7,38	2,4	5,0	- 2,2	5
5505	7,38	2,3	5,6	- 0,8	7,36	2,8	5,4	- 2,4	10
5703	7,39	3,5	4,4	- 3,8	7,40	4,8	3,0	- 7,4	¼
5704	7,40	3,7	5,7	+ 0,9	7,38	3,0	5,3	- 1,6	2
5706	7,38	2,8	4,5	- 4,0	7,38	2,7	5,9	0,0	4
5707	7,43	3,3	4,9	+ 0,5	7,40	3,6	3,9	- 4,6	10
5708	7,36	3,6	5,6	- 2,0	7,37	3,3	5,4	- 1,8	56

Table 5.9: Acid/base balance and blood gas changes during occlusion of one single median uterine artery. x = interval between onset of occlusion and moment of second blood sample.

SH	BEFORE OCCLUSION				AFTER x MIN. OCCLUSION				
	pH	PO_2 (kPa)	PCO_2 (kPa)	BE (mmol/L)	pH	PO_2 (kPa)	PCO_2 (kPa)	BE (mmol/L)	x (min)
5506	7,39	2,7	5,1	- 1,4	7,36	2,0	5,6	- 1,5	15
5508	7,34	5,0	3,8	- 8,8	7,35	1,5	3,0	- 9,8	36
					7,33	2,1	5,7	- 3,5	50
6403-T	7,38	3,1	5,4	- 1,5	7,37	2,3	6,0	- 0,7	7
6403-G	7,37	3,0	5,3	- 2,3	7,39	2,6	5,5	- 0,7	7

Table 5.10: Acid/base balance and blood gas changes during simultaneous occlusion of both median uterine arteries. Experiment 6403 involved the occlusion of both median uterine arteries in a twin pregnancy consisting of the fetal lambs SH 6403-T and SH 6403-G.

care was taken to obtain the fetal arterial blood samples in a strictly anaerobic manner and either to process them immediately or to store them at + 4° Celsius for at most 60 minutes. In spite of these precautions some suspect results were recorded in the blood sample analyses.
Values of 5.0 kPa of PO_2, as listed in tables 5.10 and 5.11, raise suspicion regarding their validity.

5.3.3 Summary of observations

- No marked changes in pH, PO_2, PCO_2 and/or BE were obtained by occluding one single median uterine artery, even during occlusions lasting as long as 60 minutes.
- Simultaneous occlusion of both median uterine arteries resulted in a mild decrease in PO_2, but other biochemical parameters did not show a consistent change.

5.4 Common internal iliac artery occlusions

A total of 56 occlusions of the common internal iliac artery was performed in 9 animals.
The duration of the occlusion ranged from 30 seconds to 30 minutes.
Suitable tracings of all cardiovascular parameters were obtained in 45 experiments. In 7 experiments a technical failure in the FECG electrodes prevented a reliable calculation of the fetal R-R interval and PEP, and in 4 experiments no suitable blood pressure tracing could be obtained due to blocking of the catheter.
In 29 experiments the autonomic nervous system was left intact, in 16 experiments parts of it were blocked pharmacologically. A steady state blood sample was drawn in each of these experiments. One or more succeeding samples, during the period of occlusion, were obtained on 23 occasions in lambs with an intact autonomic nervous system (table 5.11).
It was refrained from taking a sample during the occlusion in 15 experiments, namely those of shorter duration, in order not to interfere with the, otherwise undisturbed, fetal arterial blood pressure registration.

5.4.1 Biochemical changes

The biochemical changes induced by the occlusion of the maternal common internal iliac artery in fetal lambs with an intact autonomic nervous system are listed in table 5.11.
In two experiments, 1109 and 1111, the period of occlusion was extended beyond the time of the second blood sample to evaluate further changes in pH, PO_2, PCO_2 and Base Excess.
In SH 1109 two samples were obtained during the occlusion which lasted 12 minutes. In SH 1111 three samples were obtained during 30 minutes of occlusion.
It can be seen from these experiments that after an initial rapid decrease in pH and PO_2 (and increase in PCO_2 and base

SH	BEFORE OCCLUSION				AFTER x MIN. OCCLUSION				
	pH	PO_2 (kPa)	PCO_2 (kPa)	BE (mmol/L)	pH	PO_2 (kPa)	PCO_2 (kPa)	BE (mmol/L)	x (min)
0203	7,35	1,1	6,7	+ 0,4	7,28	1,7	5,9	- 5,8	2½
0701	7,39	4,3	5,2	- 1,0	7,37	2,5	5,2	- 2,4	5
0707	7,42	4,2	6,3	+ 4,4	7,35	2,2	6,8	+ 1,1	8
0708	7,40	4,1	6,0	+ 2,1	7,35	2,8	6,0	- 1,4	8
0717	7,39	2,8	6,4	+ 3,1	7,40	2,5	4,9	- 0,7	½
1102	7,35	2,4	6,1	- 1,1	7,33	1,3	6,3	- 1,7	2½
1107	7,33	3,6	5,8	- 3,0	7,25	--	4,9	-10,5	4½
1108	7,38	2,6	4,8	- 2,9	7,29	1,2	6,7	- 3,9	4½
1109	7,37	2,0	5,4	- 2,0	7,29	0,9	6,4	- 3,8	6
					7,26	0,7	6,0	- 6,7	10
1111	7,38	2,4	4,8	- 3,1	7,29	1,7	5,6	- 6,5	13
					7,28	1,3	6,0	- 6,0	20
					7,23	1,3	5,8	- 9,0	29
1401	7,35	4,9	3,7	- 7,7	7,33	2,6	5,3	- 4,5	4
1402	7,38	5,0	5,7	- 0,2	7,35	3,7	5,8	- 1,2	25
1501	7,41	2,5	4,8	- 0,9	7,28	1,5	6,4	- 5,1	3
1502	7,37	3,3	4,8	- 3,4	7,20	1,5	7,7	- 7,6	3
1512	7,39	2,5	5,8	+ 0,2	7,21	1,0	8,0	- 6,0	4½
1521	7,35	3,5	5,6	- 2,9	7,25	2,2	7,0	- 5,6	4½
1522	7,36	3,0	5,3	- 3,0	7,30	3,1	5,7	- 5,4	5
1524	7,36	2,5	5,1	- 3,7	7,24	0,9	6,4	- 7,4	3½
1527	7,39	4,2	4,6	- 3,4	7,28	1,3	6,6	- 5,1	4½
1528	7,35	3,8	5,1	- 3,8	7,29	2,2	5,1	- 7,6	5
1529	7,37	3,4	5,7	- 1,4	7,31	1,7	6,2	- 3,6	5
2106	7,29	3,1	5,5	- 6,8	7,16	1,7	8,2	- 8,5	8
2107	7,31	1,9	6,7	- 2,3	7,14	1,4	9,5	- 7,7	8

Table 5.11: Acid/base balance and blood gas changes during occlusion of the common internal iliac artery. SH = number of experiment; x = interval (in minutes) between onset of occlusion and moment of second blood sampling; -- = determination failed.

deficit) a more slowly progressive second decrease occurs. It can also be noted that the degree of change in biochemical parameters during the occlusion varied among the different animals. During 8 minutes of occlusion of the common internal iliac artery in experiment SH 2106, for example, the change in fetal acid/base balance and blood gases was considerably less than it was in SH 0708 during the same period of occlusion of the same vessel (table 5.11; 5.12).

	SH 2106	SH 0708	
pH	- 0.13	- 0.05	
PO_2	- 1.4	- 1.3	kPa
PCO_2	+ 2.7	0.0	kPa
BE	- 1.7	- 3.5	mmol/L

Table 5.12: Difference between arterial acid/base balance and blood gases before and after 8 minutes of occlusion of the common internal iliac artery in SH 2106 and SH 0708.

Subtracting pH values as a matter of fact is an incorrect way of expressing a change in acidity of the fetal blood ($\equiv [H^+]$).
Since it has become practice, however, to express this kind of change in "pH units", it also was done here.

Statistical analysis of the differences in blood gas values and pH between the blood samples before and during the occlusion respectively, by means of analysis of variance revealed that especially the change in pH and PCO_2 depended strongly on the experimental animal in which the determination was performed ($p = 0.006$ and $p = 0.046$ respectively).
The tail probability for the PO_2 also was relatively small ($p = 0.12$), suggesting an individual animal dependency here too.

Fetal pH fell significantly during the occlusion of the maternal common internal iliac artery ($p < 0.01$; Student's t-test for paired observations), as did the PO_2 ($p < 0.01$; t-test). The rise in PCO_2 during the period of occlusion also reached statistical significance ($p < 0.02$; t-test).

5.4.1.1 Summary of observations

- Occlusion of the maternal common internal iliac artery, and hence of the main blood supply to the pregnant uterus, was accompanied by a significant lowering of the fetal arterial pH and PO_2 ($p < 0.01$; Student's t-test for paired observations) and a rise in fetal PCO_2 ($p < 0.02$; t-test).
- The degree of asphyxia developed during the occlusion differed between the various experimental animals.
- After an initial phase of rapidly increasing asphyxia, a more slowly progressive second phase could be recognized in the two experiments in which blood samples were obtained during an extended period of occlusion.

5.4.2 Hemodynamic changes

A total of 45 suitable recordings was obtained in 7 individual fetal lambs from 56 occlusion experiments of the maternal common internal iliac artery (table 5.13).

	n exp	n anim
intact aut. nerv. sys.	29	7
atropine	6	2
phentolamine	6	3
propranolol	4	2

Table 5.13:
Summary of the common internal iliac artery occlusion experiments, according to the kind of fetal autonomic nervous system blockade; n exp = number of experiments performed; n anim = number of fetal lambs concerned.

5.4.2.1 Intact autonomic nervous system

Two occlusions, SH 1101 and SH 0716, each lasting 30 seconds, apparently were too brief to induce a change in fetal arterial blood pressure, R-R interval or PEP.
In the remaining 27 occlusions, lasting from 60 seconds to 30 minutes, a change was found in the fetal arterial blood pressure and PEP, as well as in the fetal R-R interval.
The fetal systolic and diastolic blood pressures increased invariably, starting with a varying delay after the onset of the occlusion. The relative hypertension was maintained until the end of the occlusion period (fig. 5.47; 5.48; 5.49).

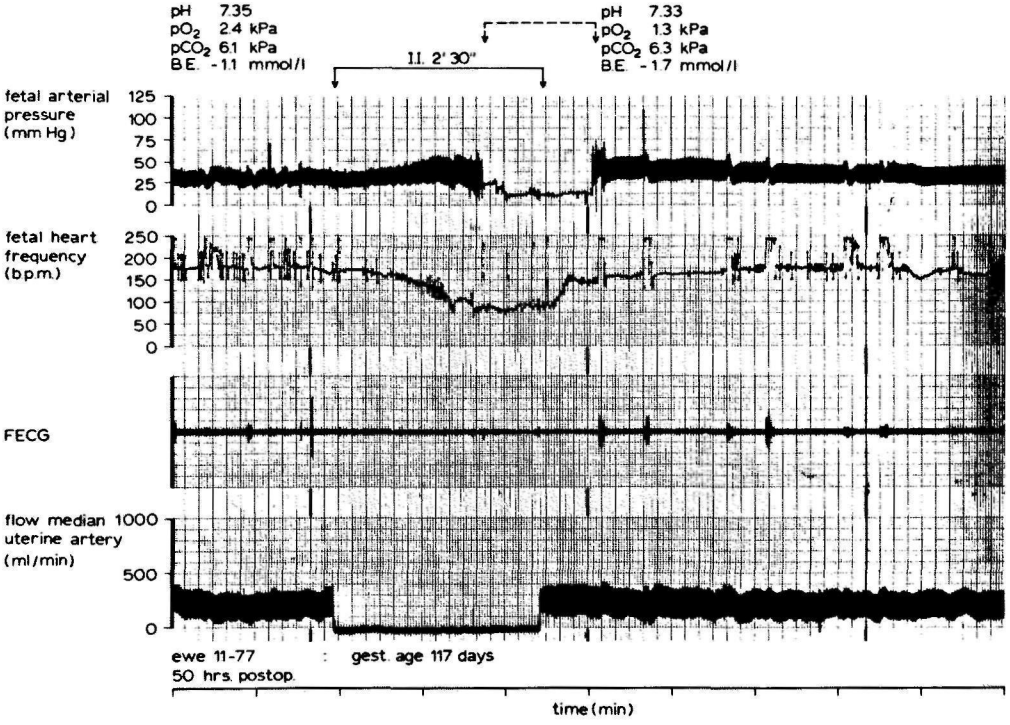


Figure 5.47: Occlusion of the maternal common internal iliac artery (II) during 150 seconds (2'30") in ewe 11-77. Results of blood sample analyses before and at the end of the occlusion are indicated at the top of the figure.

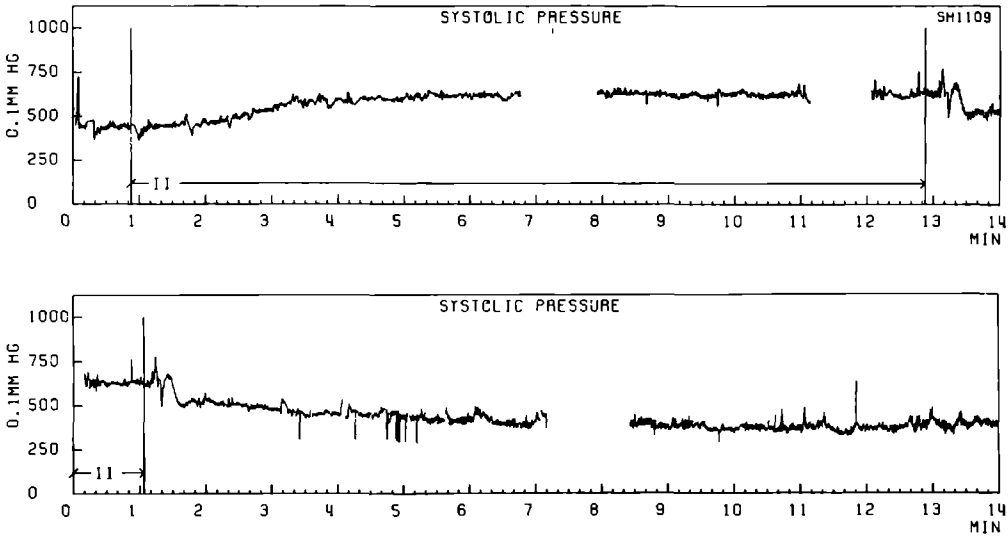


Figure 5.48: Occlusion of the maternal common internal iliac artery (II) for 12 minutes, indicated by the two vertical bars; experiment no. 9 in the fetal lamb of ewe 11-77. Blood sample results:
Pre-occlusion sample : pH 7.37 PO_2 2.0 PCO_2 5.4 BE -2.0
Sample after 6' occl. : pH 7.29 PO_2 0.9 PCO_2 6.4 BE -3.8
Sample after 10' occl.: pH 7.26 PO_2 0.7 PCO_2 6.0 BE -6.7
Post-occlusion sample : pH 7.31 PO_2 2.2 PCO_2 5.4 BE -5.1
The lower panel illustrates the recovery period. The vertical bar in the lower tracing indicates the end of the occlusion and corresponds to the second vertical bar in the upper tracing.

The initial change in fetal R-R interval was also consistent during the 27 occlusions lasting for one minute or more. The R-R interval increased (heart rate decreased) following an initial delay after the onset of occlusion in each experiment (fig. 5.50). In 11 experiments, with occlusion durations ranging from 1.0 to 6.5 minutes, the R-R interval showed no tendency to recover during the period of occlusion. In 15 other experiments, lasting from 2.5 to 12 minutes, a partial return of the R-R interval towards the pre-occlusion level was observed. In the remaining experiment (SH 1111), in which the period of occlusion was prolonged to 30 minutes, the initial bradycardia gave way gradually to a heart rate above the pre-occlusion steady state level (table 5.14).

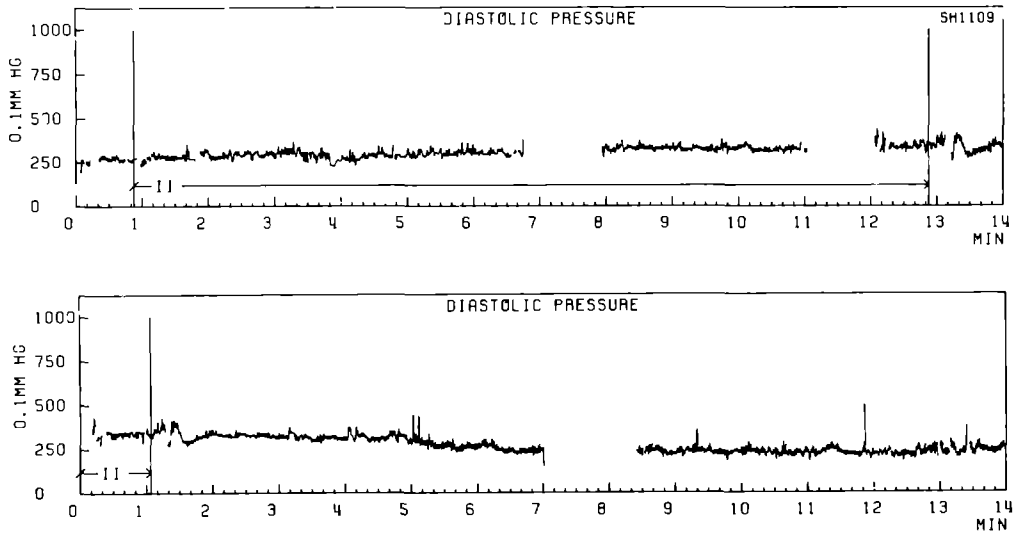


Figure 5.49: Experiment no. SH 1109: diastolic pressure. Legends as in figure 5.48.

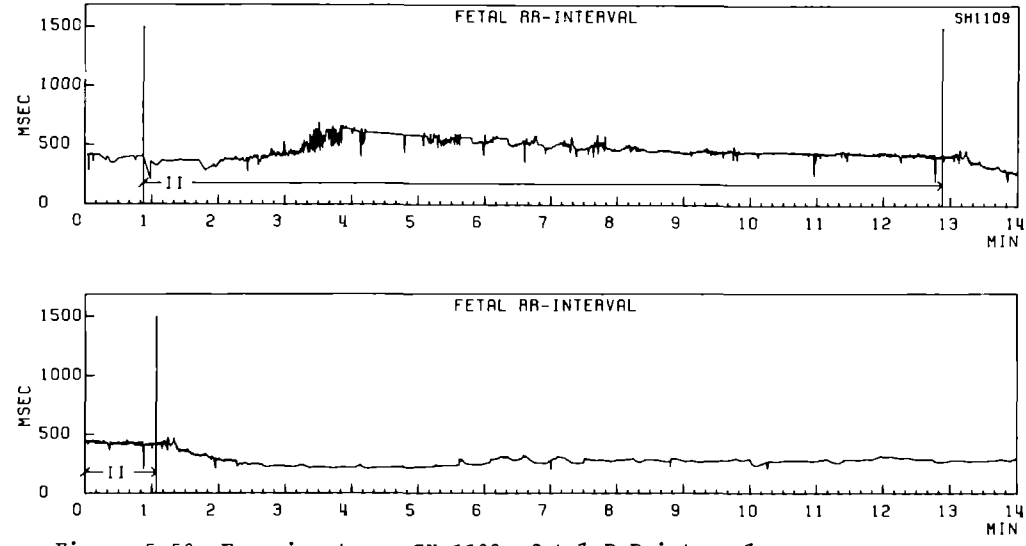


Figure 5.50: Experiment no. SH 1109: fetal R-R interval. Legends as in figure 5.48.

The fetal values for arterial blood pressures, R-R interval and PEP in experiment SH 1111, concerning a 30-minute occlusion of the common internal iliac artery, are listed in table 5.14.

time (min)	pressure syst (mmHg)	pressure diast (mmHg)	R-R interval (msec)	heart rate (b.p.m.)	PEP (msec)
start -1.0'	43	27	408	147	142
start occl.	40	25	406	148	144
+0.5'	42	27	402	149	144
+1.0'	48	28	400	150	140
+1.5'	46	26	440	136	132
+2.0'	51	27	496	121	128
+2.5'	51	26	550	109	128
+3.0'	52	25	646	93	132
+4.0'	55	26	606	99	126
+5.0'	55	24	546	110	126
+10.0'	63	35	444	135	124
+15.0'	55	33	344	174	120
+20.0'	57	39	378	159	118
end occl.	54	33	344	174	116
end +1.0'	40	25	230	260	120

Table 5.14: Blood pressures, R-R interval, heart rate and PEP during 30 minutes of occlusion of the common internal iliac artery in experiment no. SH 1111.

In an attempt to objectify the changes in the fetal PEP during the occlusion of the maternal common internal iliac artery the median value of this parameter was calculated during a 30-second steady state period before the onset of occlusion (A) and during two periods of 15 seconds each, the first immediately preceding the moment of blood sampling during the

occlusion (B), the second immediately following it (C). The change in PEP was calculated as the difference between A and half the sum of B+C. If no blood sample was obtained the difference between A and the median value during a 15-second period preceding the end of occlusion was calculated.
If regarding as a change in PEP a prolongation or a shortening of 5 msec or more, no change was observed in 9 of 29 occlusions. The interval between the onset of these occlusions and the second blood sample ranged from 0.5 to 4 minutes (table 5.15).
A prolongation of up to 27 msec was observed during 5 occlusions (fig. 5.51), their onset-to-sample interval ranging from 2.5 to 5 minutes (table 5.15).
A shortening of the PEP of up to 24 msec was found in the remaining 15 occlusions (fig. 5.52); the onset-to-sample interval in these occlusions ranged from 3.5 to 29 minutes.

	onset-to-sample interval	n
no change in PEP	0.5 - 4 minutes	9
prolongation of PEP	2.5 - 5 minutes	5
shortening of PEP	3.5 - 29 minutes	15

Table 5.15: Change in PEP in relation to duration of occlusion (between onset and moment of second blood sample).

The procedure of calculating the change in fetal PEP during the occlusion of the maternal common internal iliac artery $(A - \frac{B+C}{2})$ was also applied in the determination of the change in blood pressures and R-R interval in the 23 experiments in which a blood sample during the occlusion was obtained. Statistical analysis of the changes in systolic and diastolic blood pressure, R-R interval and PEP during the occlusion confirmed the consistency of the increases in blood pressures and R-R interval during occlusion, but did not reveal any signi-

ficant correlation between the degree of change in either of the four cardiovascular parameters and the reduced level of PO_2 and/or pH (second sample) reached during the occlusion ($p > 0.1$; Spearman's test for rank correlation).

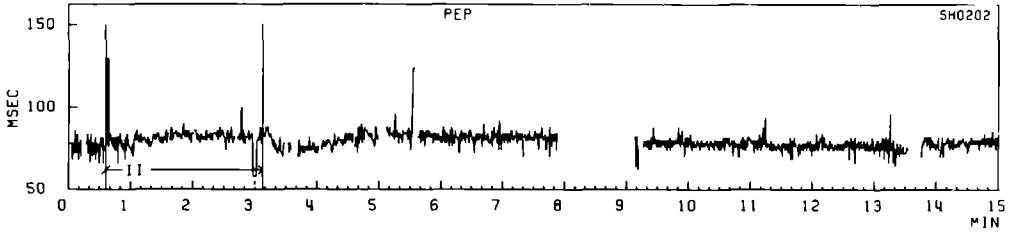


Figure 5.51: Occlusion of the common internal iliac artery (II) for 2'30", indicated by the two vertical bars; experiment no. 2 in the fetal lamb of ewe 02-77.

A considerable difference existed among the various experimental animals with respect to the interval between the onset of occlusion and the first cardiovascular parameter changes, even when the initial biochemical control values were quite comparable.

For instance, in the experiments SH 2104 and 1102, even though the steady state acid/base balance and blood gases were very similar (table 5.16), the intervals between the onset of the occlusion and the first evidence of fetal hemodynamic response were 21 and 60 seconds, respectively.

	SH 2104	SH 1102	
pH	7.35	7.35	
PO_2	2.3	2.4	kPa
PCO_2	6.9	6.1	kPa
BE	+ 1.3	- 1.1	mmol/L

Table 5.16: Acid/base balance and blood gas values during steady state conditions prior to the occlusion of the common internal iliac artery in SH 2104 and 1102.

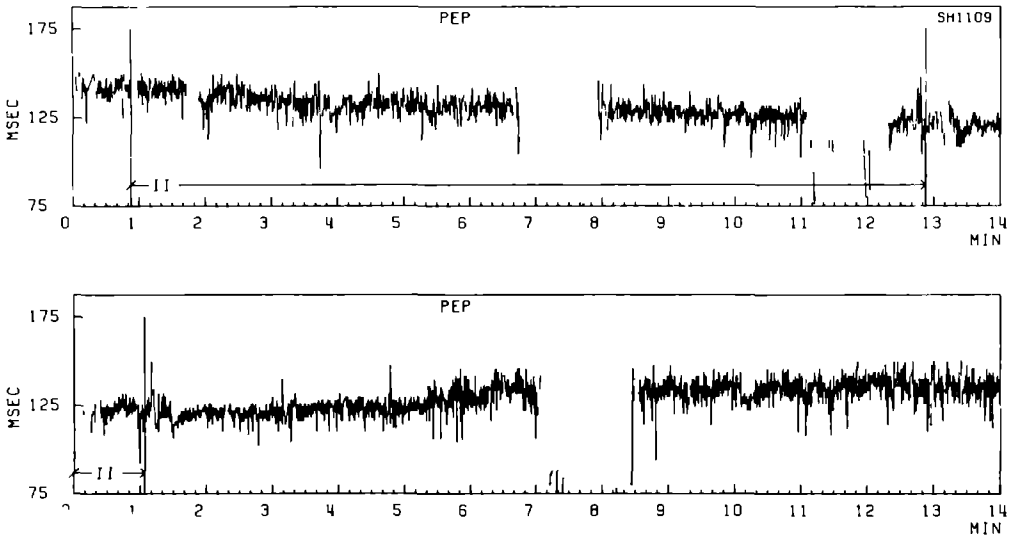


Figure 5.52: Experiment no. SH 1109: PEP. Legends as in figure 5.48.

5.4.2.2 Blockade of parts of the autonomic nervous system

In order to study the role of the autonomic nervous system in fetal adaptive regulatory responses to biochemical changes resulting from the sudden decrease in the maternal placental perfusion, parts of this system were blocked selectively by means of pharmacologic blocking agents.

5.4.2.2.1 Cholinergic blockade

When the fetal parasympathetic nervous system was blocked with atropine prior to the occlusion of the maternal common internal iliac artery, systolic and diastolic blood pressure changes accompanying the occlusion were comparable to those seen during occlusions in animals with intact autonomic nervous systems. A rise in both systolic and diastolic blood pressure was observed after an initial delay period following the onset of occlusion. In some of the experiments a slow initial increase and a more abrupt second pressure rise could be discerned (fig. 5.53; 5.54).

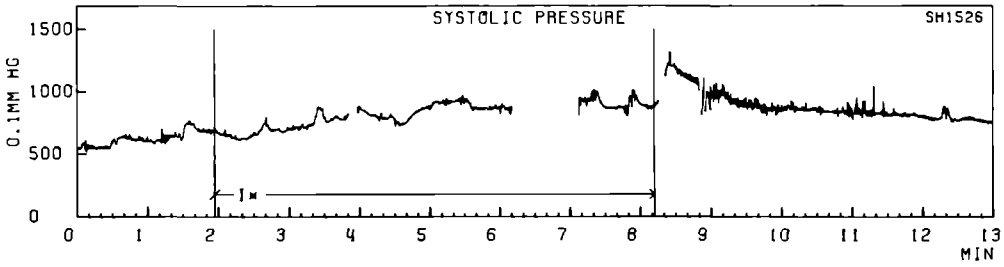


Figure 5.53: Occlusion of the maternal common internal iliac artery for 6'15", indicated by the two vertical bars, after the administration of atropine (Ix); experiment no. 26 in the fetal lamb of ewe 15-78

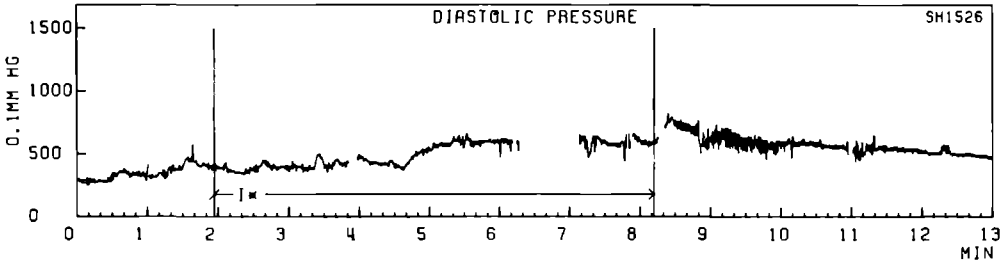


Figure 5.54: Experiment no. SH 1526: diastolic blood pressure.

After cholinergic blockade, the initial response of the fetal R-R interval to interruption of maternal placental blood flow was variable:
In three occlusion experiments, the R-R interval initially increased while in the remaining three a decrease was observed. This initial variable response was followed consistently, however, by a slow decrease in the R-R interval to between 20 and 50 msec below pre-occlusion levels during the latter part of the occlusion period (fig. 5.55), indicating mild to moderate fetal tachycardia (170-210 b.p.m.).
The onset of the decrease in R-R interval coincided with the onset of the secondary rise in fetal blood pressure during the occlusion. The duration of occlusion ranged from 6 to 13 minutes.

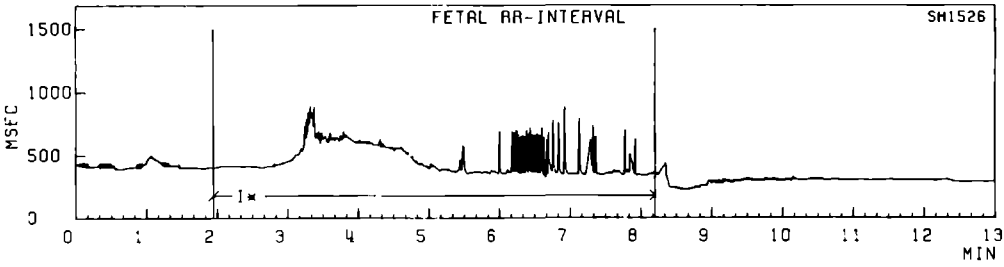


Figure 5.55: Experiment no. SH 1526: fetal R-R interval.

The PEP decreased during the occlusion in each experiment in this group (fig. 5.56). The onset of the decrease in PEP followed an initial delay period and coincided with the beginning of the increase in fetal systolic and diastolic blood pressure.

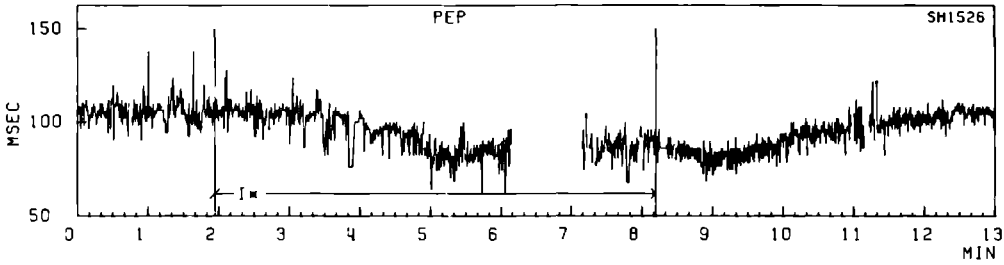


Figure 5.56: Experiment no. SH 1526: PEP.

5.4.2.2.2 Alpha-adrenergic blockade

In fetal lambs with a blockade of the alpha-adrenergic system systolic and diastolic blood pressures decreased during occlusions of the maternal common internal iliac artery (fig. 5.57; 5.58).
In the longer lasting occlusions (above 6 minutes), a recovery of fetal arterial blood pressure occurred during the latter part of the occlusion. In some of these experiments, the fetal blood pressure eventually reached levels above the pre-occlusion values (fig. 5.59; 5.60).

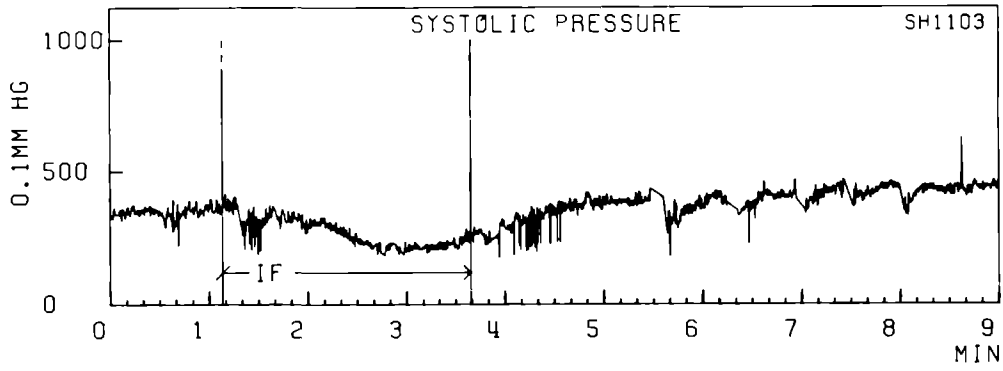


Figure 5.57: Occlusion of the maternal common internal iliac artery for 2'30", indicated by the two vertical bars, after the administration of phentolamine (IF); experiment no. 3 in the fetal lamb of ewe 11-77.

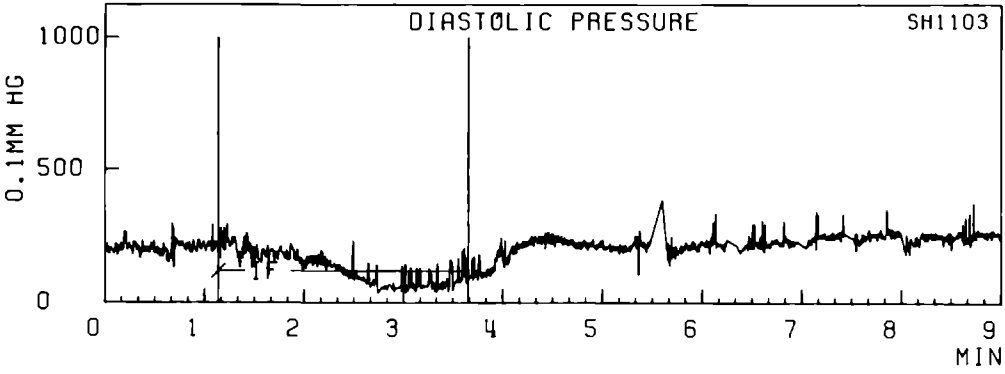


Figure 5.58: Experiment no. SH 1103: diastolic blood pressure.

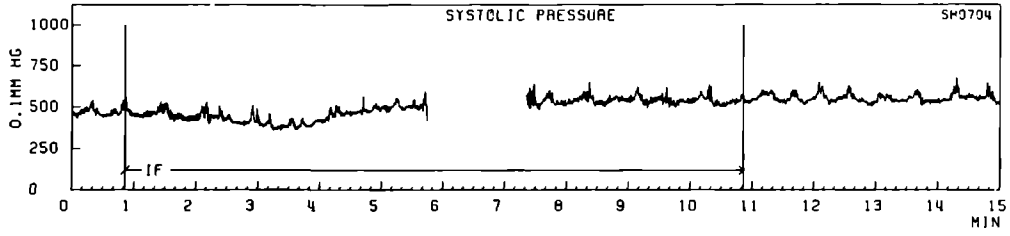


Figure 5.59: Experiment no. SH 0704: systolic blood pressure.

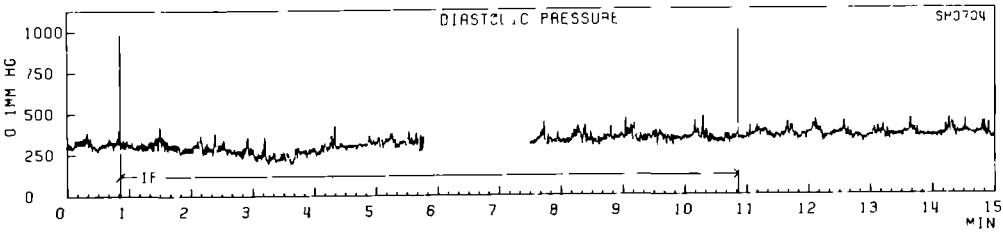


Figure 5.60: Experiment no. SH 0704: diastolic blood pressure.

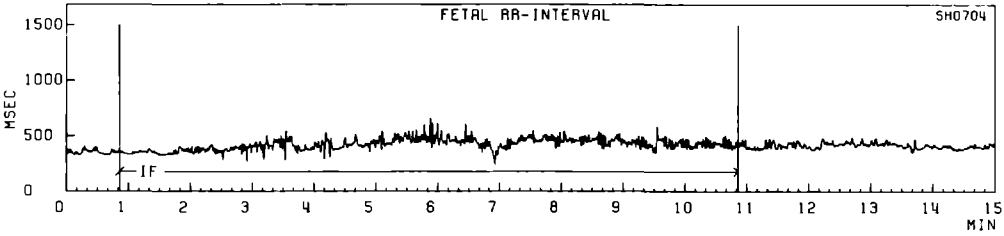


Figure 5.61: Experiment no. SH 0704: fetal R-R interval.

The R-R interval increased consistently, simultaneously with the fall in arterial blood pressure, but the change was generally of small magnitude (fig. 5.61). When a recovery of fetal arterial blood pressure occurred during the longer lasting experiments the R-R interval was found to show a simultaneous secondary partial return to the initial control level.

The PEP shortened during occlusions under alpha-adrenergic blockade (fig. 5.62), simultaneously with the above mentioned fall in blood pressure and increase in R-R interval, after the same initial delay period following the onset of occlusion. A secondary partial return to the control levels was found also in the PEP during the longer lasting occlusion experiments. The moment of onset of this secondary prolongation, however, did not coincide with the secondary changes in blood pressure but rather lagged some 60 seconds behind.

The duration of occlusion ranged from 2.5 to 10 minutes.

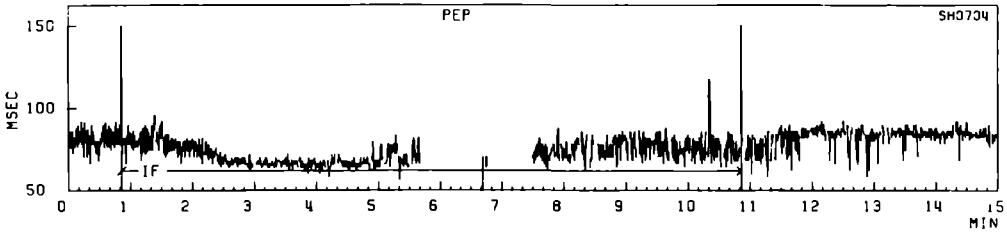


Figure 5.62: Experiment no. SH 0704: PEP.

5.4.2.2.3 Beta-adrenergic blockade

Four occlusion experiments during beta-adrenergic blockade yielded suitable tracings of the cardiovascular parameters. In 3 of these, serious rhythm disturbances and asystole, occurring after a varying period of the occlusion, prevented the calculation of PEP.
When the occlusion was released however a rapid spontaneous return of the cardiac activity was always seen.
During the complete duration of occlusion in the fourth experiment, SH 0703, and during that period of occlusion in the others during which cardiac activity existed, fetal systolic and diastolic blood pressures increased, as did the heart period. Also the PEP became increased, and remained prolonged, during the balance of the occlusion period (fig. 5.66). Never was a consistent shortening of the PEP observed, although serious degrees of hypoxemia were measured during the occlusion (PO_2 1.4 kPa).
It does not seem appropriate to draw conclusions from one single experiment, but it should be noted that the delay between the onset of occlusion and the onset of prolongation of the PEP appears to be greater than that which was observed between the onset of occlusion and the first reactions of systolic blood pressure and R-R interval (fig. 5.63; 5.65).
The diastolic pressure tracing from experiment no. SH 0703 only reveals an increase after about 8 minutes of occlusion (fig. 5.64), together with a secondary increase in systolic blood pressure, and perhaps also in R-R interval and PEP.

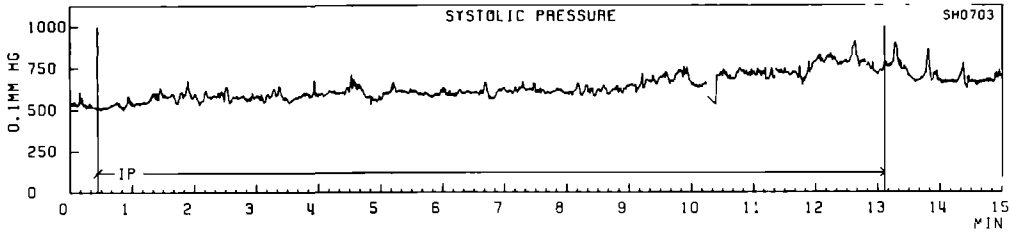


Figure 5.63: Occlusion of the maternal common internal iliac artery for 12'45", indicated by the two vertical bars, after the administration of propranolol (IP); experiment no. 3 in the fetal lamb of ewe 07-77.

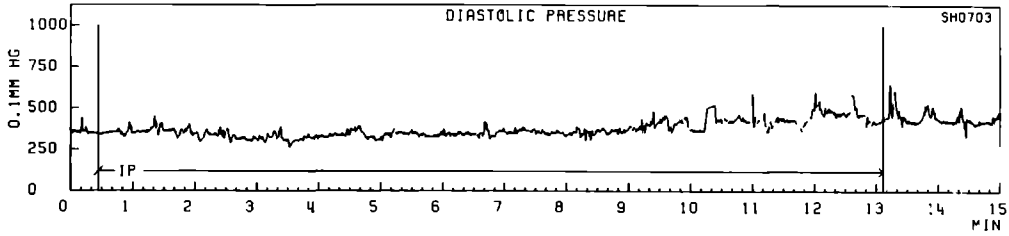


Figure 5.64: Experiment no. SH 0703: diastolic blood pressure.

The duration of occlusion ranged from 1'30" to 12'45".

A prolongation of the R-R interval (bradycardia) occurred consistently during the occlusions with a blockade of the beta-adrenergic system (fig. 5.65).

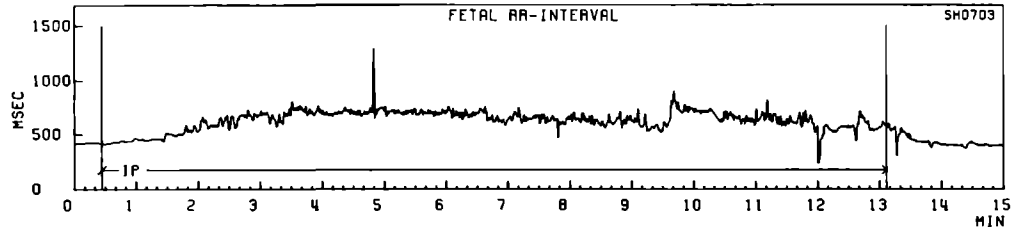


Figure 5.65: Experiment no. SH 0703: fetal R-R interval.

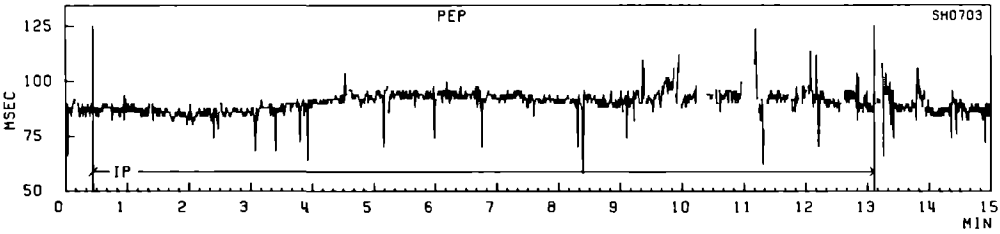


Figure 5.66: Experiment no. SH 0703: PEP.

5.4.2.3 Post-occlusion response

Two different patterns could be discerned in the post-occlusion response of the various cardiovascular parameters.

The first pattern was a slow return to the pre-occlusion steady state levels. This occurred in 8 of the 23 fetal lambs with an intact autonomic nervous system from which a blood sample was obtained during the occlusion.

Following the end of the occlusion in the remaining 15 fetal lambs a decrease in fetal R-R interval was observed to well below the initial control levels, indicating the occurrence of a post-occlusion tachycardia. This can be seen in fig. 5.50. Since this post-occlusion change in heart frequency is difficult to discern in the R-R interval tracing, the heart rate has been plotted in figure 5.67.
In 10 fetal lambs this post-occlusion tachycardia was associated with an increase in blood pressure to above the level reached during the occlusion. In 6 of the 10 instances in which both blood pressure and heart rate increased after the occlusion, there was a simultaneous shortening of the PEP.

The PO_2 reached during the occlusion in the experiments with a post-occlusion "overshoot response" ranged from 0.7 to 2.2 kPa, whereas during occlusions which showed no such response it had only fallen to between 2.2 and 3.7 kPa.

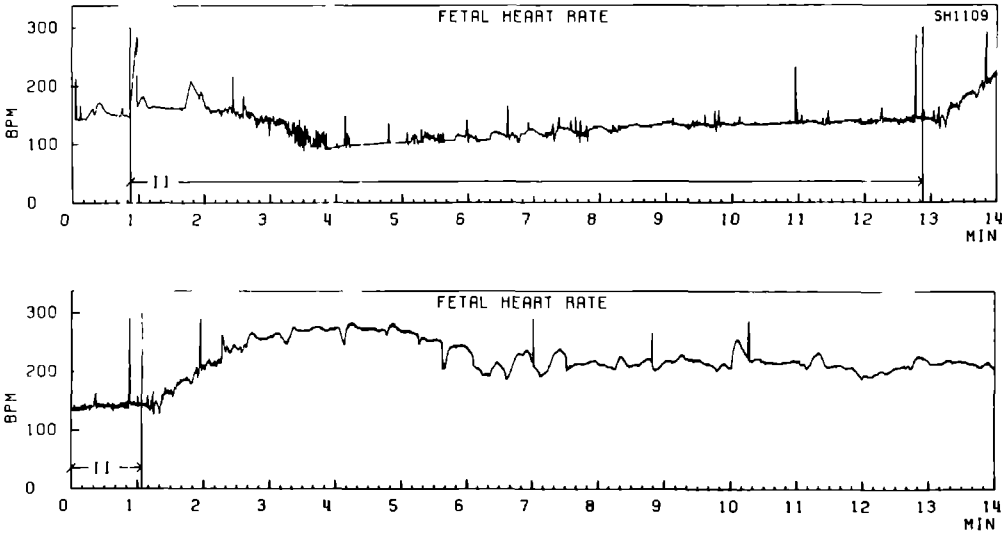


Figure 5.67: Occlusion of the maternal common internal iliac artery (II) during 12 minutes, indicated by the two vertical bars; experiment no. 9 in the fetal lamb of ewe 11-77. Legends as in fig. 5.48.

pH had decreased to between 7.14 and 7.33 in the group with an "overshoot response" and to 7.25 and 7.40 in the one without. No difference was noted in the PCO_2 reached during occlusion (4.9-9.5 kPa and 4.9-7.0 kPa, respectively) or in the duration of occlusion (2.5-30 min and 4-30 min respectively).

Although these figures suggest a relation between the occurrence of an "overshoot response" and more serious fetal hypoxemia and acidemia during the occlusion, no relation could be demonstrated between the degree of cardiovascular parameter change in the post-occlusion period and the degree of hypoxemia or acidemia attained during the occlusion.

For this purpose the difference was calculated between the median value of each single cardiovascular parameter during a 15 seconds' period one minute after the end of the occlusion and the median value during the pre-occlusion steady state. The magnitude of these differences however did not relate to the pH, PO_2 or PCO_2 measured during the occlusion.

An unsuitability of the testing method applied also can be held responsible for this lack of correlation.

In both the atropine and phentolamine blocked animals, the overshoot of heart rate and blood pressure, and the associated shortening of PEP occurred in the individuals which had become more severely hypoxemic (PO_2 below 2.2 kPa) during the occlusion, although the number of experiments in each group was too small to permit drawing general conclusions.

The administration of propranolol prevented the occurrence of a post-occlusion fetal tachycardia, whereas the PEP, which had become prolonged during the occlusion, gradually decreased to its pre-occlusion level. In no case did the PEP shorten below pre-occlusion control levels during beta-blockade in the absence of a cardiac rhythm disturbance.
The increase in blood pressure during the post-occlusion period also occurred in the beta-blocked situation. The number of experiments during selective autonomic blockade was too small to permit statistical detection of possible differences in the degree of hypertension during recovery, according to the autonomic mechanism which had been blocked.

5.4.2.4 Summary of observations

- A varying interval was observed between the onset of the occlusion of the maternal common internal iliac artery and the first evidence of fetal cardiovascular response.
- The primary response of the fetal arterial blood pressure consisted of an increase. This increase in both systolic and diastolic pressure was present till the release of the occlusion.
- The fetal R-R interval prolonged during the occlusion, reflecting the development of a fetal bradycardia. In the longer lasting occlusions a partial return of the R-R interval to its initial control level was observed; and in one experiment, SH 1111 lasting 30 minutes, the R-R interval

was found to decrease even to below its steady state level, indicating a fetal tachycardia.

- The duration of the PEP did not change at all or showed a prolongation during 14 occlusions of a short duration (0.5-5 min), but shortened during the second part of 15 longer lasting occlusions (3.5-29 min).
- No correlation was found between the degree of shortening of the PEP and the degree of hypoxemia measured during the occlusion.
- In the post-occlusion phase, a return of the various fetal cardiovascular parameters to their steady state levels was seen. A post-occlusion tachycardia was observed in fetal lambs that suffered from a particularly severe hypoxemia during the occlusion (PO_2 below 2.2 kPa). This tachycardia was accompanied in the majority (10 of 15) of cases by a simultaneous increase in fetal arterial blood pressure. Shortening of PEP occurred in six of the ten fetuses showing the blood pressure increase.
- Only minor changes in R-R interval, prolongations as well as shortenings, were seen during the initial phase of occlusion after cholinergic blockade. A tachycardia was a consistent finding during the second part of the occlusion. This tachycardia occurred notwithstanding the fact that serious degrees of asphyxia were reached in the fetal lamb according to the results of the blood gas analyses.
  In experiment no. 26 in the fetal lamb of ewe no. 15-78 (fig. 5.68) for example the PO_2 fell during the occlusion to 0.9 kPa and the pH to 7.18.
  Blood pressure rose and PEP shortened also during the occlusion experiments in fetal lambs with a blockade of the cholinergic system.
- No rise in blood pressure was seen during the occlusion in fetal lambs with a blockade of the alpha-adrenergic system. Instead a fall was observed in fetal arterial blood pressure which showed a tendency to rise again during the second part of the occlusion in the longer lasting experiments.

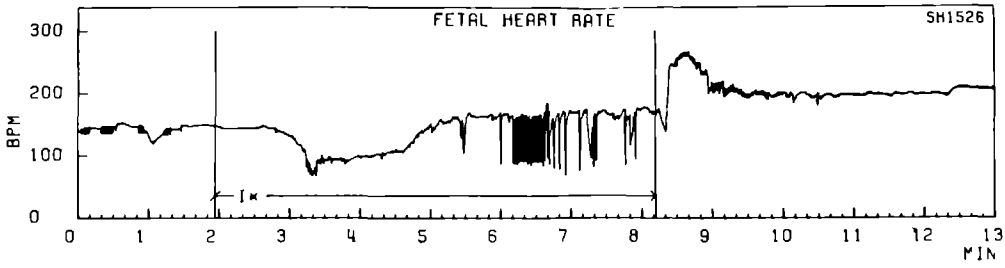


Figure 5.68: Experiment no. SH 1526: fetal heart rate.

Together with the initial fall in blood pressure the R-R interval prolonged during the occlusion but never above 660 msec (equal to a heart rate of 90 b.p.m.), even though in one occlusion the fetal arterial PO_2 fell to 1.3 kPa and the pH to 7.20. The PEP shortened also during alpha-adrenergic blockade.

- Blocking of the beta-adrenergic receptors in the fetus prevented the shortening of the PEP during the occlusion of the maternal common internal iliac artery, although serious degrees of hypoxemia were reached.
  A prolongation was seen instead, which was present till the end of the occlusion period, even when the occlusion was maintained for more than 12 minutes. The fetal arterial systolic and diastolic blood pressures increased during the occlusion and the heart period prolonged, even till a complete asystole was reached in three of the occlusions with a collapse of the arterial blood pressure.
- No qualitative differences were observed in the post-occlusion period during cholinergic and alpha-adrenergic blockade compared to the non-blocked situation, concerning the behavior of fetal arterial blood pressure, heart period and PEP. Following the occlusion during beta-adrenergic blockade no tachycardia was observed, while a post-occlusion shortening of the PEP also was never observed on these occasions. Instead a gradual decrease of the PEP was seen, from the increased level attained during the occlusion to the initial steady state control level.

SUMMARY TABULATION II:

fetal cardiovascular parameter changes during maternal common internal iliac artery occlusions and recovery.

BP = blood pressure
R-R = R-R interval
PEP = pre-ejection period
II = maternal common internal iliac artery occlusion

A = atropine
F = phentolamine
P = propranolol
↗ = increase
↘ = decrease
~ = no change

II	early occlusion	late occlusion	early recovery	late recovery
BP	↗	↗	↘ - ↗↗	↘
R-R	↗	↗	↘ - ↘↘	↘
PEP	~ - ↗	↘	↗ - ↘↘	↗
II + A				
BP	↗	↗	↘ - ↗↗	↘
R-R	↗ - ↘	↘ ↘	↘ ↘	↗
PEP	↘	↘	↗ - ↘↘	↗
II + F				
BP	↘	↘ - ↗	↗ - ↗↗	↗
R-R	↗	↗	↘ - ↘↘	↘
PEP	↘	↘ - ↗	↗	↗
II + P				
BP	↗	(↗)	(↘)	↘
R-R	↗	(↗)	(↘)	↘
PEP	↗	(↗)	(↘)	↘

The fetal arterial blood pressure also increased following the end of the occlusion during beta-adrenergic blockade. The number of suitable tracings obtained in occlusion experiments during selective autonomic blockade was too small to permit a statistical analysis of any quantitative differences in the response of the various cardiovascular parameters to the occlusion of the maternal common internal iliac artery in lambs with an intact autonomic nervous system.

CHAPTER 6

DISCUSSION

6.1 Validation of steady state registrations

The average control values for blood gases and acid/base balance in the fetal lamb during chronic experimental conditions from seven fetal research centers are listed in table 6.1, the PO_2 and PCO_2 converted into kiloPascals (1 kPa = 1 N/m^2 = 7.5 mmHg).

	pH	PO_2	PCO_2	Reference
San Diego	7.40	2.9	5.1	Kirkpatrick et al., 1973
Los Angeles	7.30	2.7	6.0	Assali et al., 1974
San Francisco	7.37	2.5	5.6	Cohn et al., 1974
New York	7.37	2.4	5.5	Daniel et al., 1975
Oxford	7.37	3.5	5.9	Jones et al., 1975
Nijmegen I	7.40	3.7	5.8	De Haan et al., 1976b
Melbourne	7.39	3.4	6.1	Maloney et al., 1977
Nijmegen II	7.37	2.8	5.8	This study

Table 6.1: Comparison of pH and blood gas values in fetal arterial blood samples during steady state conditions in chronic sheep experiments in 7 fetal research centers.

The average initial biochemical control values from the present investigation are well in accordance with those reported by other research departments. The differences between the present figures and those given by de Haan in 1976 lie within the range of the respective standard deviations.They can be explained by the difference in the number of blood samples (212 in 32 fetal lambs vs 6 in 6 fetal lambs), and by the fact that, in the 1976 report, only steady state values determined 48 hours after surgery were included, whereas in this study all of the steady state samples during the complete duration of the experimental period have been considered. These include also those obtained in fetal lambs that showed a progressive decrease in fetal oxygenation on successive days.

Comparison of the values for cardiovascular parameters from the various laboratories is more difficult. It has been shown (Weiss, 1975; Maloney et al., 1977) that there is a correlation between fetal heart rate and gestational age. The extent of the surgery and the post-operative interval allowed for recovery also influence these fetal parameters (Rudolph, 1974; de Haan et al., 1976b). In addition to the differences thus introduced by fetal age and experimental conditions, there has been little uniformity in defining (corrected) fetal arterial blood pressure or mean arterial blood pressure (e.g., whether or not blood pressures were corrected for intrauterine pressure; whether mean pressures were determined by integration or by calculation from systolic and diastolic pressures). For the frequency of fetal heart action, both the heart rate or its reciprocal value, the R-R interval, have been employed. By converting all heart periods into heart rates and all blood pressures into mean pressures (defining the latter as the sum of one third of the systolic and two thirds of the diastolic values), figures are reached as indicated in table 6.2.

	FHR (b.p.m.)	BP (mmHg)	Reference
San Diego	161	63	Kirkpatrick et al., 1973
Los Angeles	--	55	Assali et al., 1974
San Francisco	164	57	Cohn et al., 1974
New York	194	45	Daniel et al., 1975
Oxford	160	50	Jones et al., 1975
Nijmegen I	144	50	De Haan et al., 1976b
Melbourne	170	44	Maloney et al., 1977
Nijmegen II	161	44	This study

Table 6.2: Comparison of averaged fetal heart rates and mean arterial blood pressures recorded during chronic sheep experiments in 7 fetal research centers, irrespective of fetal age, time from surgery and extent of surgical procedures.

In the case of heart rate and blood pressure, the steady state values in the present study are consistent with those reported by other investigators too.

6.2 Effect of autonomic blockade on resting cardiovascular parameters

Fetal R-R interval decreased following the administration of atropine. And fetal arterial diastolic blood pressure increased. Fetal systolic blood pressure fell and R-R interval shortened when phentolamine was administered. Although not a specific subject of this study, the changes in cardiovascular parameters following the administration of selective autonomic blocking agents are in general agreement with those reported by Vapaavuori et al. (1973) and by Nuwayhid et al. (1975) in term fetal lambs. The increase in heart rate following the administration of phentolamine is likely to have had a dual action: a reflex component caused by the decrease in systemic arterial blood pressure, and the direct cardiac stimulatory property of phentolamine (Nickerson, 1949).

Barcroft (1946) postulated that it is necessary to distinguish "between the date at which the machinery of vascular reflexes is set up and that at which it is used".
Changes induced in the resting values of cardiovascular parameters by selective blockade of the autonomic nervous system thus indicate the effect of the suppression of a basal autonomic nervous tone. The absence of changes does not, however, indicate an inability of the autonomic nervous system to influence these parameters during conditions of fetal stress and distress. The fetal blood pressure and heart rate responses to the injection of autonomic drugs and autonomic blocking agents have been studied by several investigators. Evidence of autonomic activity was found already in early gestation. The responsiveness of autonomic receptors to isoproterenol, methoxamine and acetylcholine was present from 0.5 gestation (Barrett et al., 1972; Vapaavuori et al., 1973). Cholinergic and alpha-adrenergic blockade produced a maximum response between 100 and 120 days of gestation with little further change;

beta-adrenergic response developed differently, with increasing tonic activity demonstrable throughout late pregnancy and after birth (Vapaavuori et al., 1973).

The lack of a consistent change of the PEP following administration of selective autonomic blocking agents to the fetus under basal conditions is in accordance with the presumed deficiency of tonic autonomic regulation of myocardial contractility in the fetal lamb. In contrast to the adult, where regulatory impulses transmitted via the sympathetic nerves constitute one of the fundamental mechanisms for the modulation of cardiac contractility (Braunwald et al., 1963), in the perinatal period the interaction between a supersensitive myocardium (Friedman, 1972; Su et al., 1973) and the adrenal release of catecholamines (Comline et al., 1965, 1966; Jones et al., 1975) may play a more critical, compensatory role in the response of the fetus to distress. Perhaps low tonic release of catecholamines from the fetal adrenals also plays a role in the regulation of cardiac contractility. Histochemical observations by Lebowitz et al. (1972) in the fetal lamb have shown that at about 80-100 days of gestation, large nerve trunks begin to grow along the coronary arteries. The innervation of the myocardial tissue continues, especially for the sympathetic efferents, for some time after birth. A distinction should be made, however, between the existence of autonomic innervation of a given tissue and the possibility of a reaction to a stimulus by the same organ. Friedman (1972), who demonstrated the myocardial sympathetic innervation to be incomplete and functionally immature in the term fetal lamb, found that fetal cardiac tissue has a threefold lower threshold for the inotropic effects of nor-epinephrine than adult sheep cardiac tissue. Denervation hypersensitivity to autonomic neurotransmitters is a well recognized phenomenon, and perhaps the partial innervation at an early age is comparable to this situation.

It is tempting to speculate whether the effect of autonomic blockade on fetal heart rate but not on contractility indicates that the innervation of and tonic activity on the sinoatrial node is established before comparable influences on ventricular myocardium exist.

6.3 Umbilical cord occlusions

6.3.1 Changes in blood pressure and R-R interval

The fetal arterial systolic and diastolic blood pressures increased during occlusion of the umbilical veins as well as during occlusion of the umbilical arteries and the total umbilical cord. In all of the experiments performed in fetal lambs with intact autonomic nervous systems, the fetal arterial blood pressure remained at the initially increased level throughout the complete duration of occlusion, or even increased further. No decrease in blood pressure to the initial control level or lower, as reported by Kleinhout (1975) and Veth (1976) in acute sheep preparations with the fetus exteriorized, was seen in this series of experiments, suggesting that this late fall in blood pressure may have reflected compromise of the fetus resulting from acute surgical stress, exteriorization and/or disturbance of fetomaternal exchange. The blood pressure response was not altogether uniform, however, for in occlusions of the umbilical arteries (AA) and the total umbilical cord (TT), a steep pressure rise occurred immediately following the onset of the occlusion, whereas in occlusions involving the umbilical veins only, an initial transient lowering of the fetal arterial blood pressure was observed. This was most clearly apparent in the systolic blood pressure tracing. After only 3 to 5 seconds, the decrease was replaced by an increase in blood pressure. The increase in blood pressure during umbilical cord occlusion in some fetal lambs showed a more or less distinct two step pattern, the second step increase being most clearly discernible in the diastolic pressure tracing of poorly oxygenated fetal lambs.

Blocking the alpha-adrenergic division of the autonomic nervous system abolished the second step blood pressure increase and resulted in a decrease of fetal arterial blood pressure to below control levels during the second part of the occlusion.

When propranolol was administered to the fetal lamb prior to cord occlusion the fetal cardiovascular changes during the latter part of these occlusions were dominated by serious rhythm disturbances and even asystole.

Atropinization of the fetus did result in a blood pressure rise comparable to that seen in the non-blocked situation. The increase in both systolic and diastolic blood pressure did not show a significant difference between lambs with intact autonomic nervous systems and those with a cholinergic blockade.

Fetal R-R interval increased during the occlusion, also when the alpha- or beta-adrenergic system was blocked.
During cholinergic blockade no consistent change was found. The R-R interval was found to remain unchanged, show a late increase or even a decrease. A second step increase also was found in the R-R interval tracing, though less apparent, whereas also a partial return of the R-R interval to the control level sometimes was found.

6.3.2 Mechanisms of changes in blood pressure and R-R interval

There are two possible ways in which obstruction of the umbilical circulation might influence fetal cardiovascular parameters.
First, there are the hemodynamic alterations resulting directly from the occlusion of the cord. The placenta receives about 40% of the fetal cardiac output during steady state conditions in the chronic fetal lamb preparation (Rudolph and Heymann, 1970; Peeters, 1978). Thus, exclusion of the placental vascular bed from the systemic circulation and the resulting increase in peripheral resistance will exert a profound influence upon the fetal circulation. In this series of experiments, this was shown by the increase in fetal arterial systolic and diastolic blood pressures during the occlusion.
The differences in the response of the fetal circulation to

separate occlusions of the umbilical arteries and veins are explained by Veth (1976) by pointing out that after occluding the umbilical arteries (in the acute sheep preparation), blood flows out of the placenta to the fetal circulation for about 14 seconds, whereas after occlusion of the umbilical veins blood flows into the placenta for about 12 seconds. Confirmation of the latter phenomenon can be found in the umbilical artery blood flow registrations during occlusions of the umbilical veins (fig. 3.4). Following the blockade of the umbilical veins, the flow in the umbilical arteries only gradually diminished until after some 10 to 20 seconds a bidirectional flow pattern was observed with a zero mean flow. During the first few moments of occlusion of the umbilical veins a decrease in venous return is the main cardiovascular alteration (Reynolds et al., 1958; James et al., 1976). Activation of autonomic nervous system reflexes might add to the direct hemodynamic disturbance of fetal cardiovascular equilibrium by the cord occlusion.

A second way in which obstruction of the umbilical circulation might influence fetal cardiovascular parameters is by the interference with the placental exchange of oxygen and CO_2. This might either influence myocardial contractility directly by affecting myocardial energy metabolism or also have an indirect effect upon the fetal cardiovascular equilibrium by activating the fetal sympathoadrenergic system. The important role of the alpha-adrenergic part of the autonomic nervous system in the secondary cardiovascular adjustments to cord occlusion is illustrated by the decrease in systolic and diastolic blood pressure during the second part of the occlusion in lambs with an alpha-blockade. This is in agreement with the concept that a redistribution of blood flow occurs during serious hypoxemia in favor of the vital organs (heart and brain) and the placenta and at the cost of the circulation to such organs as the kidneys, small intestine, carcass, spleen and lungs (Cohn et al., 1974;

Peeters, 1978). This redistribution results from selective vasoconstriction, which in turn is thought to be mediated by the alpha-adrenergic system.
Both the first and the second step in blood pressure increase were also observed by Dawes et al. (1968) during total umbilical cord occlusions in the acute fetal lamb preparation. The first step increase occurred immediately following the onset of the occlusion and was accompanied by an increase in fetal hind limb flow. The second step occurred between 5 and 55 seconds following the onset of the occlusion and was associated with a simultaneous vasoconstriction of the fetal hind limb artery. The time lag between the onset of the occlusion and the second step in blood pressure rise was not changed by the interposition of an extracorporeal delay loop between the fetal carotid and femoral artery. The femoral vasoconstriction was abolished by cutting the sciatic nerve, the fetal hind limb's principal sympathetic supply. The authors concluded that the second step increase in blood pressure, due to the peripheral vasoconstriction, is of reflex origin.

Thus, during umbilical cord occlusion, the two main determinants of the fetal cardiovascular changes appear to be the increase in peripheral resistance due to the occlusion per se and the additional increase resulting from peripheral vasoconstriction in the course of redistribution of blood flow in response to the rapidly decreasing fetal oxygen stores.

No quantitative information is available on the possible degree of asphyxia reached during the 30 seconds of cord occlusion in the chronic animal preparation.
In the acute sheep preparation, Comline et al. (1965) found rapid rates of fall in PO_2 (15-30 mmHg/min), rise in PCO_2 (10 mmHg/min) and fall in pH (0.07/min).
Dawes et al. (1968), also in the acute sheep preparation, reported a fall in PO_2 (13 mmHg), a rise in PCO_2 (12 mmHg) and a fall in pH (0.06) during 90 seconds of complete umbilical cord occlusion (1 mmHg = 0.133 kPa).

Myers (1972) reported similar results from observations during cord occlusions in the acute monkey preparation: a fall in PO_2 (8 mmHg/min), a rise in PCO_2 (8 mmHg/min) and a fall in pH (0.05/min).

If the oxygen supply is reduced below its consumption, the fetus may utilize its oxygen "stores" and/or supply its energy needs by anaerobic glycolysis. Most oxygen is stored as oxyhemoglobin. Thus, assuming the fetal oxygen stores to be equal to the oxygen content of the red blood cells and assuming the fetal metabolic rate to be constant during cord occlusion, the decrease in PO_2 may be estimated. In these calculations, the average fetal steady state pH of 7.37 and PO_2 of 2.8 kPa (equaling 21 mmHg) found in this series of experiments were employed. Additional values were obtained from the literature:

- Oxygen capacity fetal lamb blood: 0.168 ml O_2/ml blood (Bartels et al., 1960).
- Fetal blood volume: 104 ml/kg fetal body weight (Creasy et al., 1970).

The saturation of fetal lamb Hb can be calculated from the formula developed by Battaglia et al. (1970), wherein 1.314, 0.363 and 0.305 are three fixed coefficients that define the oxygen affinity:

$$\log PO_2 = 1.314 + 0.363\ (7.40 - pH) + 0.305 \log \frac{SO_2}{1 - SO_2}$$

Substitution of PO_2 = 21 mmHg and pH = 7.37 gives: SO_2 = 0.495 (49.5%).

Since oxygen stores are equal to oxygen capacity x total blood volume x saturation, the fetal oxygen stores in the above mentioned steady state conditions can be estimated to be

$$0.168 \times 104 \times BW \times 0.495 = 8.6 \times BW \text{ (ml } O_2\text{)}$$

BW = fetal body weight in kg

The oxygen consumption in the fetal lamb during steady state conditions was calculated to be 7.85 ml O_2/kg BW.min by Battaglia et al. (1973).
Thus, during the 0.5 minute of occlusion

$$0.5 \times 7.85 \times BW = 3.9 \times BW \text{ (ml } O_2\text{) would be consumed}$$

The oxygen store at the end of the occlusion of the umbilical circulation thus would be

$$(8.6 \times BW) - (3.9 \times BW) = 4.7 \times BW \text{ (ml } O_2\text{)}$$

which would lead to an oxygen saturation of 0.269 (= 26.9%).
Assuming the pH not to change during the occlusion, this would mean

$$PO_2 = 15.6 \text{ mmHg} = 2.1 \text{ kPa}$$

If the pH were to fall at an extremely rapid rate of 0.10/min, the same sequence of calculations would result in

$$PO_2 = 16.2 \text{ mmHg} = 2.2 \text{ kPa}$$

Thus, a fall in PO_2 during the 30 seconds of occlusion of about 0.6 to 0.7 kPa (equaling 4.5 to 5.25 mmHg) is to be expected. Although these calculations can only represent crude approximations of the real change in PO_2 during the occlusion, they seem to give a reasonable reflection of the actual changes, since they are rather similar to the changes found in those occlusions where they actually were measured (table 6.3).

A brief exposure at the end of the cord occlusion to low PO_2 values is unlikely to interfere with myocardial contractility, even in fetal lambs with lower control levels of PO_2. The levels of hypoxemia at which a fetal adrenal catecholamine release

	5 min before occlusion	end of occlusion	5 min after occlusion
pH	7.36	7.35	7.30
PO_2	2.6	2.0	2.4 kPa
PCO_2	6.1	6.2	6.3 kPa

Table 6.3: Summary of the approximated mean values of pH, PO_2 and PCO_2 measured before, at the end of and 5 minutes after the umbilical cord occlusion during the 11 experiments in 3 fetal lambs listed in table 5.6.

can be expected however may be reached. Comline et al. (1965; 1966) have demonstrated in the acute sheep preparation that there are two possible ways in which fetal adrenal medullar tissue can respond to a hypoxic stimulus. In immature fetal lambs (80-120 days of gestational age) they found a release of predominantly nor-epinephrine in response to direct adrenal stimulation by hypoxia when fetal arterial PO_2 fell below 4-5 mmHg (0.5 - 0.7 kPa). In mature fetal lambs (above 140 days) a release of nor-epinephrine only was seen as an indirect response to hypoxemia, i.e. mediated by the splanchnic nerves if PO_2 fell below 12-16 mmHg (1.6 - 2.1 kPa). A further decrease of PO_2 to below 8-12 mmHg (1.1 - 1.6 kPa) produced a release of epinephrine too. The release of both catecholamines into the fetal blood stream reached a maximum below a PO_2 of 4 mmHg (0.5 kPa). Between 120 and 140 days of gestational age a transitional stage was seen where both mechanisms appeared to be active. The adrenal catecholamine release was independent of fetal arterial PCO_2, pH or lactic acid concentration (Comline et al., 1965; 1966).

Jones et al. (1975) confirmed the occurrence of this fetal adrenal catecholamine release in the chronically instrumented fetal lamb during hypoxemia. They showed that within 10 to 25 minutes following the onset of maternal hypoxemia, a rise in fetal plasma levels of nor-epinephrine and epinephrine could

be detected. They could not confirm a specific sequence in the release of the two catecholamines. Although the mean PO_2 fell to only 18 mmHg (2.4 kPa), small amounts of nor-epinephrine as well as epinephrine appeared in the fetal circulation; however, nor-epinephrine always reached considerably higher levels than did epinephrine.

The degree of hypoxemia reached during the umbilical cord occlusions in the present series of experiments certainly is deep enough to elicit a fetal adrenal catecholamine release, especially in those fetuses which already are poorly oxygenated at the moment of occlusion (2.2 to 2.7 kPa to reach Comline's limits, and 3.0 kPa to reach Jones'). Whether these catecholamines can already exert a measurable influence during the short period of occlusion depends predominantly on the velocity of adrenal catecholamine release.

The last factor that should be considered in the discussion of fetal cardiovascular readjustments during cord occlusion is the excitation of fetal chemoreceptors, predominantly located in the aortic arch and in the carotid artery. Dawes et al. (1969) showed the aortic chemoreceptors to be operative in the last third of gestation in the fetal lamb. Reducing carotid PO_2 from 40 to 20 mmHg (5.3 - 2.7 kPa) caused a rise of arterial blood pressure and femoral vasoconstriction. These changes were unaffected by bilateral section of the nerves from the carotid sinus and body, whereas they were abolished by section of the vagi or aortic nerves. The action of these, and possibly other, chemoreceptors is rapid. It might very well represent the first line of defence in fetal blood gas homoiostasis. The findings of Dawes et al. (1968), described earlier, regarding the origin of the two step increase in fetal arterial blood pressure during total cord occlusion are well in accordance with the concept of a rapid (5-55 sec) chemoreceptor response to hypoxemia. The importance of the short term chemoreflex influence upon cardiovascular readjustments during umbilical cord occlusion is emphasized by the highly significant correlation which was

demonstrated in the present series of experiments between the PO_2 value during the pre-occlusion steady state and the increase in diastolic blood pressure during the subsequent occlusion of the umbilical circulation ($p = 0.003$; Spearman's test for rank correlation).

6.3.3 PEP changes

PEP increased immediately following the onset of occlusion, irrespective of the type of occlusion, venous, arterial or total cord. A second step also was observed in the prolongation of the PEP during the occlusion of the umbilical cord. It was associated with the simultaneous increase in fetal arterial blood pressure and occurred only in poorly oxygenated fetal lambs (PO_2 below 2.2 kPa, with one exception).
The change in PEP during the occlusion did not show a significant difference when the cholinergic system was blocked. During alpha-adrenergic blockade, however, the PEP shortened to below its control level during the second part of the occlusion, simultaneously with the decrease in fetal arterial blood pressure. When propranolol was administered to the fetal lamb prior to the occlusion, the PEP invariably became prolonged during that period of occlusion in which it could be measured. Serious rhythm disturbances and asystole in the latter part of these occlusions prevented further measurement of the PEP.

6.3.4 Mechanisms of PEP changes

Occlusion of the umbilical arteries resulting in an abrupt increase in peripheral resistance and blood pressure (Veth, 1976) prolongs the PEP directly by the increase in diastolic aortic blood pressure or afterload (Harris et al., 1966; Harris et al., 1967a). The increase in PEP found right from the start of the occlusion of the umbilical veins can be explained by the sudden decrease in venous return (Reynolds et al., 1958)

which, by decreasing the end diastolic ventricular pressure and volume (Kirkpatrick et al., 1976), will cause a decrease in myocardial contractility (Garrard et al., 1970) in accordance with the Frank-Starling mechanism. This has been shown to operate in the term fetal lamb (Brinkman et al., 1972; Kirkpatrick et al., 1976). A second mechanism which is suggested to influence the duration of the PEP (Harris et al., 1967b) is the inhibition of myocardial contractility by parasympathetic activity (Martin et al., 1969), resulting from the baroreceptor reflex which is functional in the fetal lamb during the last third of gestation (Maloney et al., 1977).
This, however, could not be confirmed in the present investigation. No significant difference in the prolongation of the PEP was found when the results from occlusions with and without cholinergic blockade in the same fetal lambs were compared ($p = 0.36$; Wilcoxon's two sample test).
The second step increase in the prolongation of the PEP during the occlusion is attributed to the simultaneous second step increase in afterload, reflected in the second step in fetal arterial blood pressure rise and most probably resulting from an additional, chemoreceptor reflex-induced, peripheral vasoconstriction (Dawes et al., 1968). The importance of changes in afterload in the determination of the duration of the PEP is stressed by the shortening of the PEP simultaneous with the decrease in blood pressure during the second part of the occlusion after alpha-adrenergic blockade. This also demonstrates the active role of alpha-adrenergic vasoconstriction in the maintenance of blood pressure and in the second step increase in fetal arterial blood pressure and PEP during the occlusion. Probably the increase in afterload is not the only factor influencing the behavior of the PEP during the occlusion. Although the degree of increase in diastolic blood pressure (afterload) was proportional to the PO_2, measured in the steady state blood sample, the prolongation of the PEP during the occlusion was not. Presumably also some beta-adrenergic stimulation of the heart takes place. This, however,

apparently never was strong enough to shorten the PEP during the period of occlusion, i.e. never a decrease in the duration of the PEP was observed despite a prolonged blood pressure rise. This is attributed to the findings of Wennergren in the cat (Wennergren, 1975; Wennergren et al., 1976) that a strong baroreceptor stimulation can suppress completely even an intense chemoreceptor impulse. The suppression of excitatory cardiac chemoreflex stimulation by simultaneous potent inhibitory baroreflex impulses was also demonstrated by Levy et al. in the canine isovolumetric left ventricle preparation (Levy et al., 1969).

No results of chronic animal studies involving the effect of umbilical cord occlusion have been published yet. Organ et al. (1973b) and Morgenstern et al. (1977) reported prolongation of the PEP during cord occlusion in the acute sheep preparation. The decrease in the duration of the PEP during the second part of the occlusion probably is due to the acute character of Morgenstern's experiments, and thus would be comparable to the decrease in blood pressure observed by Kleinhout (1975) and Veth (1976) in their acute experiments.

Organ et al. (1974), Klõck et al. (1977) and Zacutti (1977) observed a prolongation of the PEP in human fetuses during labor when heart rate patterns suggested cord occlusion.

Summarizing the results of this study, the prolongation of the PEP during the occlusion of the umbilical circulation in the fetal lamb is attributed to a combination of factors:

1. The increase in afterload (diastolic aortic blood pressure) accompanying the increase in peripheral resistance produced by the exclusion of the placental vascular bed from the fetal circulation.
2. The decrease in preload resulting from the decrease in venous return, especially when the umbilical veins are occluded.
3. An additional increase in afterload accompanying the peripheral vasoconstriction which is part of the redistribution of blood flow in favor of the vital organs (heart and brain) and the placenta during hypoxemia.

6.4 Post-occlusion period

6.4.1 Changes in blood pressure and R-R interval

Following the release of the occlusion, a transient dip was observed in the fetal arterial systolic and diastolic blood pressures. After 5 to 10 seconds the blood pressure increased again, in some experiments to levels above those attained during the occlusion. Subsequently a gradual decrease in the blood pressure to pre-occlusion levels occurred. The R-R interval which had become increased during the occlusion, gradually returned to the control level together with the return of the blood pressure.

No significant correlation was found between the recovery of both blood pressure and R-R interval during the post-occlusion period and the state of fetal oxygenation at the moment of occlusion, compared to their respective control values.

During cholinergic blockade the post-occlusion response of the blood pressure was comparable to that observed following the cord occlusion in fetal lambs with an intact autonomic nervous system. The R-R interval however decreased rapidly to below the pre-occlusion level, reflecting fetal tachycardia.

Following the occlusion during alpha-adrenergic blockade a slow increase of the fetal arterial systolic and diastolic blood pressures to their initial control level was observed, whereas the R-R interval decreased more rapidly, sometimes even to below normal.

Beta-adrenergic blockade was associated with serious rhythm disturbances during the end of the occlusion, which also were found during the first part of the post-occlusion period. Blood pressure increased during the post-occlusion period and the R-R interval only slowly returned to normal again. Never was a post-occlusion tachycardia noted during beta-blockade.

6.4.2 Mechanisms of changes in blood pressure and R-R interval

Dawes et al. (1968) attribute the initial dip in the fetal arterial blood pressure after the release of the cord occlusion to a reactive hyperemia in the peripheral tissues as a result of the preceding partial ischemia. Probably the suddenly diminished total peripheral resistance after release of the clamping, as the placental vascular bed is returned "on line", is an additional factor contributing to this transitory fall in fetal arterial blood pressure.
Dawes et al. (1968) suggest a prolonged vasoconstriction, due to circulating vasoconstrictor substances, to be the reason for the secondary blood pressure rise during the post-occlusion period. Veth (1976) attributed the great increase in arterial pressure after releasing the cord occlusion to a spasm of the umbilical arteries. Spasm of the umbilical vessels in response to tactile stimuli in fact is a common finding in acute sheep experiments with the fetus exteriorized.
A spasm of the umbilical vessels is hardly ever seen when the fetus is left in utero. Yet, also in the present series of experiments the post-occlusion pressure rise was observed. This will be discussed further in section 6.4.4.

6.4.3 PEP changes

Following the end of occlusion, a rapid shortening of the PEP occurred, on some occasions even below steady state levels. The shortening of the PEP reached its minimum simultaneously with the secondary increase in the blood pressure. Subsequently a return of the PEP to control levels was observed, either slowly by a gradual prolongation starting from the post-occlusion minimum (fig. 5.5), or more rapidly, crossing the control level again and subsequently decreasing together with the decrease in blood pressure (fig. 5.15).
The first mechanism appeared to occur by preference in poorly oxygenated fetal lambs. This was tested by calculating the

difference between PEP 30 seconds following the end of occlusion and the PEP control level, and relating this difference to the initial steady state control values of PO_2 and pH. A weak positive correlation was found between this difference in PEP and the control PO_2 ($p = 0.053$; Spearman's test for rank correlation) and pH ($p = 0.064$; Spearman's test), indicating that the more insufficient is the fetal oxygenation at the moment of occlusion (low PO_2, low pH), the shorter is the PEP during the post-occlusion period.
During cholinergic blockade a consistent shortening of the PEP during the post-occlusion period occurred in every experiment. Following the release of the occlusion during alpha-adrenergic blockade the PEP, which had become shortened already during the occlusion, returned slowly to normal, together with the blood pressure. Beta-adrenergic blockade prevented shortening of the PEP during the post-occlusion period. Instead, a prolongation of the PEP was seen, gradually returning to control levels.

6.4.4 Mechanisms of PEP changes

In contrast to the theories describing prolonged vasoconstriction or spasm of the umbilical arteries as the main determining factors in the fetal post-occlusion response, the results of the present study suggest that the cardiovascular changes during the post-occlusion period can be explained more readily by an improvement in the fetal cardiac function, resulting in a rise in cardiac output. This either can be attributed to the fact that the fetal heart receives well-oxygenated blood again after reestablishment of the umbilical circulation, but most probably also to direct sympathoadrenergic stimulation, which might have been suppressed partially during the occlusion by the strong baroreceptor reflex. The dissociation between blood pressure and PEP during the post-occlusion period adduces an argument in support of beta-adrenergic mechanisms in the recovery from cord compression. Also the fact that the

fetal arterial blood pressure increases after the occlusion along with the fetal heart rate, demonstrates that the baroreceptor reflex is overridden during this period of the experiment, either by autonomic nervous cardiac stimulation alone, or also by circulating catecholamines released by the fetal adrenals.

The suggestion of beta-adrenergic mechanisms playing an active role during the post-occlusion period is further supported by the observations during the post-occlusion period in lambs whose autonomic nervous systems had been blocked pharmacologically. A manifest fetal post-occlusion tachycardia was found during cholinergic blockade; no shortening of the PEP was observed during recovery when the beta-adrenergic system was blocked. The gradual post-occlusion return of blood pressure and PEP during alpha-adrenergic blockade demonstrates the role of alpha-adrenergic vasoconstriction in the secondary blood pressure rise during recovery, and further emphasizes the role of blood pressure in the PEP changes.

The finding of a consistently shortened PEP during the post-occlusion period after cholinergic blockade is still puzzling. An explanation may be found in the inhibition of negative chronotropic and inotropic effects of parasympathetic cardiac regulatory mechanisms. Since this, however, could not be demonstrated to affect the duration of the PEP during the occlusion, it seems unlikely that it should affect the PEP during recovery. A second possibility is the increased cardiac oxygen consumption during cholinergic blockade, due to the increased cardiac beating frequency. Whether this can result in a faster rate of oxygen debt contraction of the fetus during occlusion and thus increase the sympathoadrenergic stimulation needs further investigation.

Summarizing, it is suggested that sympathoadrenergic stimulation is a prominent feature in the fetal lamb's post-occlusion cardiovascular readjustments. In contrast to the changes during

occlusion, which are principally determined by changes in the fetal heart's loading conditions, either direct or reflex, the changes during recovery suggest a preponderance of enhanced cardiac stimulation due to either only nervous, or also humoral beta-sympathetic impulses.

Regarding the behavior of the PEP, the main determining factors appear to be

1. Increase in myocardial contractility due to beta-adrenergic stimulation.
2. Increase in afterload (diastolic blood pressure) due to alpha-adrenergic stimulation.
3. Decrease in afterload due to release of the cord and possibly also reactive hyperemia of the peripheral tissues.
4. Increased cardiac oxygen supply after reestablishment of the umbilical circulation.

The correlation, though weak, that was found between the degree of shortening of the PEP during the post-occlusion period and the state of fetal oxygenation (PO_2, pH) at the moment of occlusion suggests the first factor to be the most important one.

Venous return was not measured during the present series of experiments. The role of changes in preload following the release of the cord clamping only can be guessed. An increase in venous return, possibly enhanced by constriction of the venous capacitance vessels may also contribute to the post-occlusion shortening of the PEP.

Occlusion of the maternal iliac artery, the main vessel supplying blood to the pregnant uterus in the ewe, resulted in a significant change in blood gas values and acid/base balance (table 5.11).The mean values before occlusion and during occlusion are listed in table 6.4.

	before occlusion m ± S.E.M.	during occlusion m ± S.E.M.	
pH	7.36 ± 0.01	7.28 ± 0.03	
PO_2	3.1 ± 0.4	2.0 ± 0.3	kPa
PCO_2	5.5 ± 0.3	6.7 ± 0.4	kPa

Table 6.4: Summary of the approximated mean values of fetal pH, PO_2 and PCO_2 measured before and during the occlusion of the maternal common internal iliac artery during the 23 experiments in 6 fetal lambs listed in table 5.11.

Fetal arterial PO_2 and pH showed a statistically significant decrease during the period of occlusion of the maternal common internal iliac artery ($p < 0.01$; Student's t-test); PCO_2 increased significantly ($p < 0.02$; Student's t-test).
The most rapid rate of decrease in fetal arterial PO_2 that could be calculated from the present series of experiments amounted to 0.6 kPa/min (in SH 1401; SH 0717; SH 1502; SH 1527; see table 5.11). During umbilical cord occlusions the fall in PO_2 was calculated to be 0.6 kPa during 30 seconds of occlusion. The degree of lowering of the fetal oxygen tension, however, differed considerably among the individual lambs (tail probability, calculated by analysis of variance: $p = 0.12$).
This will be due in part to the difference in the period of occlusion. Most probably, however, also the varying extent of accessory blood supply via the cranial uterine arteries, originating from the non- occluded spermatic arteries, and via

the collateral circulation through the vessels of the pelvic wall is responsible for the differences.

6.5.1 Changes in blood pressure and P-R interval

Fetal arterial systolic and diastolic blood pressures increased after a varying delay time following the onset of occlusion. This rise in blood pressure was present till the end of occlusion, even when this was maintained for 30 minutes. The initial reaction of the fetal R-R interval to occlusion of the maternal common internal iliac artery was a prolongation (reflecting bradycardia). In the longer lasting experiments, however, a partial return to the steady state level occurred, and in one experiment lasting 30 minutes, even a mild tachycardia was observed during the last part of the occlusion. No significant correlation was found between the degree of change of either of the fetal cardiovascular parameters during the occlusion and the degree of hypoxemia, measured in the sample obtained during the occlusion.
Administration of atropine either completely prevented the occurrence of a bradycardia or reduced the degree of heart rate slowing during the occlusion of the maternal common internal iliac artery. In some experiments,a tachycardia was observed during the occlusion when vagal influences upon the heart were blocked. Fetal arterial blood pressure rose during the occlusion, also after cholinergic blockade. Blockade of the alpha-adrenergic response by phentolamine prevented the increase in fetal arterial blood pressure during the occlusion of the maternal common internal iliac artery. Instead, a fall in fetal blood pressure was observed. The fetal R-R interval increased also when peripheral vasoconstriction was prevented pharmacologically. During occlusions after the administration of propranolol fetal arterial blood pressure and R-R interval increased. Rhythm disturbances and asystole also were found during these occlusions following blockade of the beta-receptors.

Fetal cardiovascular responses to hypoxemia have been studied under a variety of laboratory conditions ranging from acute, stressed, anesthetized, exteriorized animals to chronically instrumented, non-stressed fetal lambs in utero with ample recovery periods allowed after surgery. These widely varying experimental conditions are undoubtedly responsible for the lack of uniformity in the reported fetal cardiovascular reactions to hypoxemia. Those investigators, however, who studied the fetal lamb in utero during well-defined chronic conditions have consistently described a rise in fetal arterial blood pressure and bradycardia as the primary fetal responses to hypoxemia (Cohn et al., 1974; Jones et al., 1975; Berman et al., 1976; Peeters, 1978). Cohn et al. (1974) stated that the fetal arterial blood pressure rose higher, and the heart rate fell deeper, when hypoxemia was associated with acidemia. Thus, the present observations regarding the fetal heart rate and blood pressure responses to common internal iliac artery occlusion agree with the findings of other investigators. Berman et al. (1976) noted a vagal type of bradycardia following occlusion of either the maternal descending aorta or the inferior vena cava in the chronic sheep experiment. Künzel et al. (1975) had noted the same phenomenon following reduction of uterine blood flow by occlusion of the maternal vena cava in acute experiments on sheep. A significant delay was noted in both studies between the onset of uterine blood flow reduction and the onset of fetal bradycardia, as in the present series of experiments. Both groups of investigators attributed this delay to the time required for development of a serious degree of fetal hypoxemia and the resulting fetal cardiovascular adjustments. The varying extent of accessory oxygen supply by the non-occluded cranial uterine arteries and possible anastomoses between the uterine vascular bed and maternal abdominal wall vessels should be added to the other factors influencing the delay in the onset of fetal hyperten-

sion and bradycardia.
The fall in fetal arterial blood pressure during occlusions after alpha-adrenergic blockade, the rise during beta-blockade and the occurrence of a blood pressure rise without a significant change in heart rate during the initial phase of occlusion after cholinergic blockade, indicate alpha-adrenergically induced peripheral vasoconstriction to be the main determining factor in fetal readjustments during hypoxemia, with the fall in heart rate as a secondary response mediated via the baroreceptor reflex. The fetal heart rate, however, decreased also when peripheral vasoconstriction was prevented pharmacologically, suggesting that, besides the baroreflex action secondary to the peripheral vasoconstriction, an additional cardiac slowing effect remained operative, possibly mediated via central or peripheral chemoreceptors. The occurrence of bradycardia even in the shorter occlusions during alpha-blockade suggests that direct depression of myocardial chronotropism by hypoxia was not involved. Moreover, the fetal arterial blood pressure was maintained at the same high level during hypoxemia in the non-blocked condition, further mitigating direct hypoxic depression of the heart. For the same reason, a coronary chemoreflex (Bezold-Jarisch reflex) seems improbable.
Additional beta-adrenergic chronotropic cardiac stimulation by catecholamines released from the fetal adrenals (Comline et al., 1965; 1966; Jones et al., 1975) can be held responsible for the (partial) recovery of the fetal heart rate during the second part of the longer lasting occlusions. No partial recovery but rather asystole was observed during the second part of the occlusion following beta-adrenergic blockade.

6.5.3 PEP changes

The reaction of the fetal PEP to the occlusion of the maternal common internal iliac artery was variable. In the occlusions of shorter duration (14 of the 29; duration 0.5-5 minutes), either a small prolongation or no change in the PEP was found.

In the longer lasting occlusions (15 of the 29; duration 3.5 to 29 minutes), however, a shortening of the fetal PEP was invariably recorded, even though diastolic hypertension was present. No correlation was found between the degree of PEP shortening and the degree of hypoxemia reached during the occlusion.
The PEP shortened during occlusions after cholinergic blockade. Administration of phentolamine was also associated with a shortening of the PEP during the occlusion, simultaneously with the fall in blood pressure, even during occlusions of short duration.
During occlusions following blockade of the beta-receptors by means of propranolol no shortening of the PEP was found during the complete duration of occlusion. Instead the PEP was prolonged. This prolongation persisted till the release of the clamping, even if the occlusion was maintained as long as 12 minutes, and even though serious degrees of hypoxemia were reached. During asystole, however, no PEP could be calculated of course.

6.5.4 Mechanisms of PEP changes

Organ et al. (1973b) and Morgenstern et al. (1977) reported a shortening of the PEP during fetal hypoxemia in the acute sheep preparation. A shortening of the PEP in the human fetus during labor was reported by Organ et al. (1974) and by Zacutti (1977) when heart rate patterns suggested fetal hypoxemia.
The results obtained in the present investigation agree with those reported by the cited authors. Murata et al. (1978a), however, reported both hypoxemia alone (PO_2 17-25 mmHg) and hypoxemia associated with acidemia (PO_2 14-25 mmHg, pH 6.99-7.25) to be accompanied by a prolongation of the PEP.
These investigators suggest interspecies differences in the relative sympathetic and parasympathetic responses to hypoxia, or differences in the adrenergic responsiveness of the fetal

heart to be an explanation, although perhaps unsatisfactory, of the noted disagreement. It should be noted however that no extreme degrees of hypoxia were reached in Murata's experiments, although the relative importance of the fall in fetal PO_2 is obscured by the fact that the average initial control levels of PO_2 (3.3-5.7 kPa) in their chronically instrumented fetal monkeys are higher than those reported in fetal lambs (2.4-3.7 kPa; table 6.1). Perhaps an interspecies difference in direct and indirect (i.e. splanchnic nerve mediated) fetal adrenal responsiveness to hypoxemia, as reported by Comline et al. (1966) for such seemingly comparable creatures as the fetal lamb and calf, can also explain the noted differences in PEP changes during hypoxemia between fetal lamb and monkey. Changes in sympathoadrenergic regulation were suggested to be the main determining factors in the fetal lamb's cardiovascular response to hypoxia (section 6.5.2). The effects of these changes and the resulting cardiovascular readjustments can be understood best in terms of the dual adrenergic receptor hypothesis of Ahlquist (1948). Activation of the alpha-adrenergic receptors produces vasoconstriction (Ariëns, 1970) and prolongation of the PEP results as a consequence of the resulting hypertension (Raab et al., 1958; Harris et al., 1967a). Activation of the beta-adrenergic receptors causes cardiac stimulation and vasodilatation (Ariëns, 1970). Shortening of the PEP results from the enhanced inotropism.

A shortening of the PEP was seen after administration of epinephrine to adult human subjects by Harris et al. (1967a), whereas the same investigators observed the effect of nor-epinephrine on the pre-ejection period to depend on the relative proportion of beta- and alpha-adrenergic responses elicited. They suggest that the alpha-adrenergic effect of nor-epinephrine on the vessel wall is predominant at the lower dosage levels, while its beta-adrenergic effect on the myocardium becomes increasingly prominent at higher doses (Harris et al., 1967a). The initial short term response of the fetal lamb to progressive hypoxia possibly consists primarily of a chemoreceptor-induced

increase in sympathetic efferent activity producing peripheral vasoconstriction in the course of a redistribution of blood flow to the vital organs (Dawes et al., 1968).
In the term fetal lamb this will soon be followed, however, by a rise in circulating catecholamines resulting from direct and, depending on the part played by the splanchnic nerves, indirect response of the fetal adrenal medulla to hypoxemia (Comline et al., 1965; 1966; Jones et al., 1975).
Jones et al. (1975) reported a detectable rise in circulating endogenous catecholamines within 10 to 25 minutes after the onset of hypoxemia. Dawes et al. (1968) sectioned the sciatic nerve in fetal lambs and observed a decrease in fetal hind limb blood flow during hypoxemia produced by cord occlusion after 60-100 seconds. They also attributed this effect to a rise in circulating catecholamines released by hypoxic, direct and indirect, stimulation of the adrenal medulla.
It is presumably this second effect that determines the shortening of the PEP during the longer lasting occlusions.
If the secondary fetal response to hypoxemia is indeed dominated by adrenal nor-epinephrine release, irrespective of whether this catecholamine is released earlier during progressive hypoxemia (Comline et al., 1965; 1966) or whether the plasma levels attained by nor-epinephrine are higher than those of epinephrine (Jones et al., 1975), the high levels of nor-epinephrine and of the even more beta-active epinephrine during serious hypoxemia will cause a shortening of the PEP. It is assumed that in the occlusion experiments of a shorter duration and during the initial phase of the longer lasting occlusions, either an insufficient degree of hypoxemia was reached (no change in PEP) or only a low level of alpha-adrenergic stimulation by sympathetic efferents, perhaps in combination with some nor-epinephrine release, resulted (prolongation of the PEP).The theory of increased beta-adrenergic activity being the cause of the shortening of the PEP during the latter part of occlusion is supported by the finding in the present investigation of a prolongation of the PEP during

occlusions after selective beta-adrenergic blockade.
The rapid simultaneous decrease in fetal arterial blood pressure and PEP during the first phase of the occlusion after alpha-adrenergic blockade, emphasizes the role of the alpha-adrenergic division of the nervous system - and possibly also of low levels of circulating nor-epinephrine - in the initial response of the fetal lamb to hypoxemia.
The fast increase in direct responsiveness of the fetal lamb's adrenal medulla to hypoxemia between 80-90 days of gestation and term, and the very rapid change in the splanchnic nerve mediated secretion rate of catecholamines after 130-140 days of gestation (Comline et al., 1966), can be held responsible for the lack of a significant correlation between the degree of hypoxemia reached during occlusion in the various fetal lambs and the shortening of the PEP in the respective experiment. No indication was found for a possible inhibiting effect of progressive degrees of hypoxemia upon myocardial contractility.

Summarizing, the results of this investigation confirm the findings in other chronic sheep studies that a rise in fetal arterial blood pressure and a fall in fetal heart rate are prominent features of the fetal adaptation to hypoxemia. The fetal lamb's cardiovascular adjustments to biochemical changes caused by occlusion of the maternal common internal iliac artery appear to be determined during the initial phase of occlusion by a chemoreceptor reflex-induced peripheral vasoconstriction mediated by the adrenergic nervous system. This condition is comparable to that observed during the latter part of the umbilical cord occlusions. The interaction between a supersensitive fetal myocardium (Friedman, 1972; Su et al., 1973) and the adrenal release of catecholamines may play a dominant role during the second part of occlusion in the longer lasting experiments.

Regarding the PEP the main determining factors appear to be

1. Increase in peripheral resistance and diastolic blood pressure (afterload) in the course of redistribution of blood flow during the occlusions of short duration and during the initial period of the longer lasting occlusions.
2. Overriding of this effect by an increase in myocardial contractility due to rising levels of catecholamines released by the adrenal medulla in the latter part of the longer lasting occlusions.

6.6 Recovery from internal iliac artery occlusions

6.6.1 Changes in blood pressure and R-R interval

Two different patterns of change in fetal blood pressure and R-R interval were observed following the release of the maternal common internal iliac artery clamping. In 8 (of 23) fetal lambs only a gradual return of blood pressure and heart rate to their pre-occlusion level was noted. The PO_2 measured during the occlusion in these fetal lambs ranged from 2.2 to 3.7 kPa. In the remaining 15 fetal lambs a post-occlusion fall in R-R interval was found, indicating a relative fetal tachycardia. This was associated in 10 instances with a post-occlusion rise in blood pressure to above the level reached during the occlusion. In all of the 15 fetuses showing such an "overshoot response" the PO_2 had fallen to below 2.2 kPa during the occlusion.
Also following occlusions during cholinergic and alpha-adrenergic blockade an "overshoot" in fetal heart rate and blood pressure occurred in the individuals which had become more severely hypoxemic (PO_2 below 2.2 kPa) during the occlusion. The administration of propranolol prevented the occurrence of a post-occlusion fetal tachycardia. The increase in blood pressure during the post-occlusion period also occurred in the beta-blocked situation. It still remains a puzzling fact why the asystole which so often occurred during the latter part of these occlusions, "spontaneously" passed when the clamping was released, whereas no effective circulation existed any more to transport the well-oxygenated blood to the fetus again.

6.6.2 Mechanisms of changes in blood pressure and P-R interval

Probably because most of the occlusions of the common internal iliac artery were maintained until serious degrees of hypoxemia could be presumed to be present, the post-occlusion changes

in cardiovascular parameters suggested an active recovery process, rather than a passive return of the various cardiovascular parameters to their initial control levels. The rise in fetal heart rate following the end of the occlusion, on some occasions associated with a blood pressure rise, suggests that the post-occlusion readjustments of the fetal circulation are mainly under the influence of a relative preponderance of the beta-adrenergic drive during this phase of the experiment, most probably due to the total withdrawal of afferent chemoreceptor discharge following the rapid restoration of fetal blood gas tensions after reestablishment of the maternal placental circulation.
The "active" character of the post-occlusion readjustments was stressed by the results of the occlusion experiments during selective autonomic nervous system blockade: blocking of the beta-adrenergic receptors abolished the post-occlusion tachycardia, whereas relatively high levels of tachycardia were found following the occlusion during cholinergic or alpha-adrenergic blockade.

6.6.3 PEP changes

The PEP which had become shortened during most of the occlusions returned to its initial control level again following the release of the clamping. In 6 of the occlusions showing an "overshoot response" in fetal arterial blood pressure and heart rate an additional shortening of the PEP was noted in the early recovery phase simultaneously with the "overshoot" in blood pressure and heart rate. No qualitative differences were noted in the post-occlusion pattern of PEP response between fetal lambs with intact autonomic nervous systems or with either cholinergic or alpha-adrenergic blockade. Propranolol prevented the initial shortening of the PEP during the post-occlusion phase. Instead a prolongation of the PEP was observed, which only slowly decreased to the pre-occlusion level. The determination of the PEP during the early post-

occlusion period however was often prevented by serious rhythm disturbances and asystole .

6.6.4 Mechanisms of PEP changes

The decrease in afterload due to the withdrawal of chemoreceptor discharge following the restoration of well-oxygenated blood supply to the fetus and perhaps also Dawes' phenomenon of reactive hyperemia, together with the relative preponderance of still circulating catecholamines, are to be held responsible for the additional shortening of the PEP during the early post-occlusion period in fetal lambs which suffered from severe degrees of hypoxemia (PO_2 below 2.2 kPa) during the preceding occlusion.
When apparently no catecholamines had been released during the occlusion, or when their level was too low, the PEP returned to its pre-occlusion level more gradually, together with the decrease in fetal arterial blood pressure and R-R interval. The recovery pattern of PEP change observed under selective autonomic blockade emphasizes the role of the beta-adrenergic system in the active adjustments of the circulation at this time, and in the accompanying changes in PEP.

Summarizing, the results of this investigation suggest the changes in fetal cardiovascular parameters following the release of the occlusion of the maternal common internal iliac artery to be determined by a shift in balance between the chemoreceptor reflex induced alpha-adrenergic vasoconstriction and the cardiac stimulation by circulating catecholamines. Whether the restoration of well-oxygenated blood supply to the fetal heart also is a contributing factor remains unclear. No indication was found, however, during the occlusion that hypoxemia might decrease directly fetal cardiac activity.

Regarding the PEP the main determining factors during the post-occlusion period appear to be

1. Decrease in afterload (diastolic blood pressure) once the supply of well-oxygenated blood to the fetus has been reestablished.
2. Increase in myocardial contractility due to the effect of circulating catecholamines.

The remarks made earlier, regarding the possible changes in venous return following the cord occlusions, hold also here. Sympathoadrenergic stimulation resulting in an increase in venous vascular tone may establish an additional PEP-shortening factor during the post-occlusion period.

APPENDIX I

STATISTICAL METHODS

1. Testing of changes in blood gas values (pH, PO_2, PCO_2) induced by occlusion of the umbilical cord or the maternal common internal iliac artery and of changes in the steady state values of the cardiovascular parameters (blood pressures, PEP, R-R) due to selective blocking of the autonomic nervous system. In these cases first a one way analysis of variance was employed in order to ascertain whether there was a significant animal effect on the changes or not. If this effect was not significant it was assumed that there was no individual animal dependency (that observations performed on the same animal were statistically independent) and Student's t-test for paired observations was employed to test whether the mean change was significantly different from 0. If the animal effect was significant, an approximate t-test was performed, based on the average value of the mean changes for each animal involved divided by an estimate for the standard deviation of this average value. The number of degrees of freedom was equal to the number of animals minus 1. The results of these tests, whether an animal effect was established or not, should be considered with reserve as they were based on relatively small numbers of observations performed on only a few animals and sometimes distributed unevenly over the animals. Moreover, the following assumptions are to be made, which can not be verified:
   (a) the various experiments within each individual animal are independent of each other and do not show a trend,
   (b) the probability distribution of the changes is the normal distribution.
2. In all other cases (where data of experiments on a sufficiently large number of animals were available) so-called distribution free (or nonparametric) methods were employed.

A possible individual animal dependency of the observations is always taken into account by computing a nonparametric statistic for each animal separately and testing a (weighted) average of these statistics according to the principle of the combination of independent statistical tests based on a linear combination of the test statistics (Rümke et al., 1961). Two types of combined tests were employed:

1. *the combined Wilcoxon two sample test* (Mann and Whitney U-test) in order to test the significance of the difference between observations in two separate groups of experiments with and without intervention (e.g. regarding the effect of blocking agents on the resting values of cardiovascular parameters, section 5.2.2.2). For each animal the ratio of the Mann-Whitney U-statistic and its expected value is obtained. The statistic of the combined test is the average value of these ratio's over the animals.
2. *the combined Spearman rank correlation test* in order to test the correlation between pairs of variables (e.g. between changes in cardiovascular parameters during occlusion on one side and steady state values of blood gases on the other, section 5.2.2.1.4). The statistic of the combined test is the average value of the Spearman rank correlation statistics computed for each animal separately ($\bar{r}_s$).

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APPENDIX II

SYNOPSIS OF EXPERIMENTS

1. Umbilical cord occlusions

ewe	G.A.	exp.per.	AA	A*	AF	AP	VV	V*	VF	VP	TT	T*	TF	TP
69-75	126	9	1	4	0	0	2	1	0	0	3	2	0	0
78-75	133	3	3	1	0	0	1	0	0	0	1	0	0	0
80-75	131	3	0	0	0	0	1	0	0	0	0	0	0	0
82-75	138	11	1	1	0	0	4	2	0	0	3	3	0	0
83-75	131	3	1	0	0	0	1	0	0	0	1	0	0	0
93-75	130	5	1	0	0	0	1	1	0	0	2	0	0	0
94-75	130	5	0	0	0	0	2	4	0	0	0	0	0	0
58-76	131	5	1	0	0	0	1	0	0	0	1	0	0	0
68-76	133	4	1	0	0	0	0	0	0	0	0	0	0	0
72-76	135	3	0	0	0	0	1	0	0	0	0	0	0	0
84-76	132	3	1	0	0	0	1	0	0	0	0	0	0	0
86-76	130	4	2	0	0	0	3	0	0	0	1	0	0	0
69-77	127	11	1	0	4	3	2	0	4	3	1	0	3	2

2. Umbilical cord occlusions; blood gas recording only

ewe	G.A.	exp.per.	AA	VV	TT
96-76	123	6	2	3	2
97-76	112	2	0	2	0
98-76	126	4	1	1	0

3. Maternal median uterine artery occlusions

ewe	G.A.	exp.per.	U	UU
55-77	101	8	3	2
57-77	100	11	5	0
64-77	106	5	0	2

4. Maternal common internal iliac artery occlusions

ewe	G.A.	exp.per.	II	I*	IF	IP
02-77	120	6	2	0	0	0
14-77	126	5	2	1	0	0
21-77	132	6	4	0	0	0
11-77	115	12	7	0	1	0
06-77	115	3	1	0	0	0
07-77	125	12	4	0	1	1
15-78	122	21	9	5	4	3

ewe = sheep code; first two digits indicating ewe no. , digits behind dash indicating year of experiment
G.A. = gestational age at the moment of surgery
exp.per.= duration of experimental period in days
U = occlusion of one single maternal median uterine artery
UU = occlusion of both median uterine arteries simultaneously
Other abbreviations used cf. glossary

SUMMARY

THE CARDIAC PRE-EJECTION PERIOD DURING PRENATAL LIFE

The present study deals with an investigation of the behavior of the pre-ejection period of the fetal cardiac cycle during two distinct forms of (sub)acute distress, studied in the chronically instrumented fetal lamb preparation:

1. umbilical cord occlusions,
2. maternal common internal iliac artery occlusions.

A specially constructed device permitted the occlusion of either both umbilical veins, or of both umbilical arteries, or of the total umbilical cord, with the fetal lamb under nearly physiological conditions in the ewe's womb.
A commercial type vessel occluder was employed in the occlusions of the maternal common internal iliac artery, the main blood supplying vessel to the pregnant uterus.
Experiments were started between 24 and 72 hours following surgery and continued for several days or weeks with a frequency of 1 to 3 occlusions a day.

A prolongation of the PEP together with an increase in blood pressure was a consistent finding during occlusions of the umbilical cord, both during occlusions of the umbilical arteries and of the total cord as well as during occlusions of the umbilical veins. Also in the umbilical vein occlusions the PEP prolonged right from the start of the occlusion notwithstanding the fact that in the fetal arterial blood pressure a transient, initial fall could be observed during the first 3 to 5 seconds of occlusion. In poorly oxygenated fetal lambs a two step increase in the duration of the PEP was observed during the occlusion, which was accompanied by a simultaneous two step increase in fetal arterial blood pressure.
Following the end of the occlusion a shortening of the PEP was observed, even to below the pre-occlusion level. The degree of shortening of the PEP, in relation to the control level,

appeared to be related to the state of fetal oxygenation at the moment of occlusion.
During occlusion the main determining factors of the PEP prolongation appear to be the increase in afterload and the decrease in preload of the fetal heart, whereas an increase in myocardial contractility is suggested to be the principal cause of shortening of the PEP in the post-occlusion period.
The second step in the prolongation of the PEP during the occlusions in poorly oxygenated fetal lambs is attributed to a chemoreceptor-induced reflex, resulting in a redistribution of blood flow.

Occlusion of the maternal common internal iliac artery produced a fall in PO_2 and pH and a rise in PCO_2. Fetal arterial blood pressure increased and PEP shortened, especially in the longer lasting occlusions. Fetal heart rate exhibited a bradycardia also during this type of occlusion. A gradual return of the PEP to its initial control level was observed after the end of occlusion. In fetal lambs which had become severely hypoxemic during the occlusion an additional shortening of the PEP was observed during the onset of the post-occlusion period prior to the return to normal of this parameter. This additional PEP-shortening was associated with a so-called "overshoot response" in fetal blood pressure and heart rate. An increase in myocardial contractility due to rising levels of catecholamines released by the fetal adrenal medulla during hypoxemia is suggested to be the principal cause of the shortening of the PEP during maternal common internal iliac artery occlusions, whereas a gradual decrease in afterload is held responsible for the return to normal of the PEP once the supply of well-oxygenated blood to the fetus has been reestablished.

SAMENVATTING

DE CARDIALE PRE-EJECTIE PERIODE TIJDENS HET PRENATALE LEVEN

Het onderwerp van dit proefschrift wordt gevormd door een onderzoek naar het gedrag van de pre-ejectie periode van de foetale hartcyclus tijdens twee vormen van (sub)acute noodsituaties, bestudeerd in het zogenaamde chronische schapepreparaat:

1. afklemmingen van de bloedvaten in de navelstreng
2. afklemmingen van de moederlijke a. iliaca interna communis.

Door middel van een speciaal daartoe ontworpen instrument was het mogelijk de navelstrengvaten af te klemmen, terwijl het foetale lam zich onder nagenoeg fysiologische omstandigheden bij de ooi in de baarmoeder bevond. De navelstrengarteriën en de navelstrengvenen konden afzonderlijk of in combinatie worden afgeklemd.
Een commerciële vaatafsluiter werd toegepast om de moederlijke a. iliaca interna communis af te klemmen. Via dit vat vindt het grootste gedeelte van de moederlijke bloedtoevoer naar de zwangere baarmoeder plaats.
Met de experimenten werd gestart 24 tot 72 uur na de operatie. De frequentie bedroeg 1 tot 3 afklemmingen per dag gedurende de experimenteerperiode, welke per schaap variëerde, van enkele dagen tot maximaal 3 weken.

Een verlenging van de PEP, tezamen met een stijging van de foetale bloeddruk werd steevast waargenomen tijdens afklemmingen van de navelstreng. Dit gold voor elk der 3 types afklemmingen, t.w. van de navelstrengvenen, van de navelstrengarteriën en van alle vier de navelstrengvaten gezamenlijk. Tijdens afklemmingen van de navelstrengvenen vond er eerst een kortdurende, voorbijgaande daling van de foetale arteriële bloeddruk plaats gedurende 3 tot 5 seconden, aansluitend aan het begin van de afklemming. Tijdens de andere twee types afklemmingen steeg de

foetale bloeddruk meteen. De foetale hartfrequentie daalde in de beide laatste gevallen meteen na het begin van de afklemming en bij de veneuze afklemmingen met enige vertraging.
De PEP nam onmiddellijk toe vanaf het begin der afklemming, ongeacht het feit of het een afklemming van de venen, van de arteriën of van de totale navelstreng betrof. Bij foetale lammeren met een lage arteriële zuurstofspanning op het tijdstip van de afklemming werden twee afzonderlijke fases waargenomen in de toename van de PEP tijdens de afklemming. Een overeenkomstige tweetraps-stijging werd onder die omstandigheden tijdens de afklemming gezien in de foetale arteriële bloeddruk.
Na het einde van de afklemming verkortte de PEP, soms zelfs tot beneden het niveau van voor de afklemming. De mate van verkorting van de PEP ten opzichte van haar oorspronkelijke duur bleek samen te hangen met de zuurstofvoorziening van het foetale lam op het tijdstip van de afklemming.
De verlenging van de PEP tijdens de afklemming wordt toegeschreven aan de toename van de afterload en de afname van de preload van het foetale hart ten gevolge van de uitsluiting van het placentavaatbed uit de foetale circulatie. De tweede trap in de stijging van de PEP bij slecht geoxygeneerde lammeren wordt geduid als het effect van een chemoreceptorreflex (redistributie van de bloedvoorziening). Een toename in de contractiliteit van het foetale hart wordt gezien als de voornaamste oorzaak voor de verkorting van de PEP na afloop van de afklemming.

Occlusie van de moederlijke a. iliaca interna communis bracht een afname van de foetale arteriële PO_2 en pH met zich mee; de PCO_2 steeg. Met name tijdens afklemmingen van langere duur (5 minuten en meer) verkortte de PEP terwijl de foetale arteriële bloeddruk toenam. De foetale hartfrequentie liet ook tijdens deze occlusies een bradycardie zien.
Een geleidelijke terugkeer van de PEP naar haar oorspronkelijke niveau werd gezien na het opheffen der afklemming. Een extra-

verkorting ging aan dit herstel van de PEP vooraf bij die foetale lammeren, welke in ernstige zuurstofnood gebracht waren tijdens de afklemming. Deze extra PEP-verkorting werd vergezeld door een zogenaamde "overshoot response" van de foetale arteriële bloeddruk en hartfrequentie. Een toename van de myocard contractiliteit onder invloed van de stijgende hoeveelheid catecholamines welke door het foetale bijniermerg tijdens zuurstoftekort worden uitgescheiden wordt gezien als de belangrijkste oorzaak voor de PEP-verkorting tijdens de belemmering van de moederlijke bloedtoevoer naar de placenta. De afname van de afterload van het hart lijkt de voornaamste bepalende factor in het herstel van de PEP wanneer het foetale zuurstofaanbod weer eenmaal op peil gebracht is na het einde der afklemming.

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1949	Geboren te Roermond op 25 september
1961 - 1967	Middelbare schoolopleiding aan het St.Thomas-college der paters Augustijnen te Venlo.
1967	Eindexamen gymnasium-beta.
1967 - 1975	Studie geneeskunde aan de Katholieke Universiteit te Nijmegen.
1970	Onderzoek op het gebied der inspanningsfysiologie aan het instituut voor humane fysiologie, Universiteit van Milaan (hoofd: Prof. Dr. R. Margaria).
1974 - 1975	Co-assistentschappen te Nijmegen, Heerlen, Arnhem, 's Hertogenbosch, Roermond en Tanzania.
1975	Arts-examen
1975 - 1977	Militaire dienst; werkzaam als 1^{o} luitenant op de 834 HKR te Nijmegen.
1975 - 1978	Onderzoek naar de betekenis van de PEP in het Nijmeegs chronisch schape-project.
1977 - heden	Opleiding tot vrouwenarts in de Universiteitskliniek voor Obstetrie en Gynaecologie van het St. Radboud-ziekenhuis te Nijmegen (hoofden: Prof. Dr. T.K.A.B. Eskes, Prof. Dr. J.L. Mastboom).

Stellingen

behorend bij het proefschrift

"The cardiac pre-ejection period during prenatal life"

Nijmegen, 8 juni 1978 Hans Evers

I

De tweede trap in de toename van bloeddruk en PEP tijdens afklemming van de navelstreng bij slecht geoxygeneerde foetale lammeren benadrukt de rol van perifere vasoconstrictie in de aanpassing van de foetus aan hypoxemie.

Dit proefschrift

II

Het verkorten van de PEP, simultaan met het stijgen van de foetale bloeddruk, tijdens occlusies van de maternale zijde van de placenta-circulatie bij het schaap vormt een ondersteuning van de theorie van Comline en Silver dat tijdens ernstige hypoxemie catecholamines worden afgegeven door het bijniermerg van het foetale lam.

Comline, R.S., Silver, M., (1961): J.Physiol. 156: 424 - 444.
Dit proefschrift

III

Dat een foetale bradycardie tijdens hypoxemie ook optreedt na blokkering van het alpha-adrenerge deel van het autonome zenuwstelsel verwijst naar de rol van andere dan enkel de baroreceptoren in de regulatie van de hartfrequentie bij het foetale lam.

Dit proefschrift

IV

Verlenging van de PEP tijdens de antepartum periode is in een groot aantal gevallen indicatief voor het ontstaan van foetale nood tijdens de partus.

Murata, Y., Martin, C.B., (1974): Obstet. Gynecol. 44: 224 - 232.

V

De conclusie van Rudolph en Heymann, dat het foetale lam in utero niet in staat is om bij bradycardie het slagvolume van zijn hart dusdanig te verhogen dat een constant hartminuutvolume gehandhaafd wordt, berust op onvoldoende feitelijke gegevens.

Rudolph, A.M., Heymann, M.A., (1976): Am. J. Obstet. Gynecol. 124: 183 - 192.

VI

De conclusie van Kirkpatrick et al., dat het foetale lam in utero wel in staat is om bij bradycardie het slagvolume van zijn hart dusdanig te verhogen dat een constant hartminuutvolume gehandhaafd wordt, kan een verklaring vormen voor het tekort aan eenduidigheid waarmee foetale nood kan worden gedetecteerd door middel van registratie van het foetale hartfrequentiepatroon.

Kirkpatrick et al., (1976): Am. J. Physiol. 231: 495 - 500.

VII

Corrosie van koperen hoogspanningsleidingen onder invloed van aggressieve industriële schoorsteengassen, en de daaruit resulterende verhoging van het kopergehalte van gras en grond, maakt het onverantwoord in sterk geïndustrialiseerde gebieden schapen nog langer in de nabijheid van deze kabels te weiden.

VIII

Tegelijk met de toename in het aanbod van passief amusement aan de Venlose burgerij, met name via de talloze ter plaatse te ontvangen televisiezenders, is het karakter van haar actieve participatie in de traditionele viering van de *"vastelaovend"* veranderd.

IX

Het couperen van de schapestaart strekt dit in esthetisch opzicht toch al karig bedeelde dier niet tot voordeel.

Dit proefschrift: frontpagina en pagina 51.

X

Een mens dient zijn eerste verjaardag drie maanden postpartum te vieren.

XI

Het situeren, door buitenlandse hulporganisaties, van eilanden van westerse gezondheidszorg op het platteland van Tanzania is niet in overeenstemming met het streven van de regering van deze Oostafrikaanse republiek naar een geregionaliseerde low cost medical care.

XII

De horizontale positie tijdens de baring is een, voor discussie vatbare, concessie van de vrouw aan de verloskundige. Het is op zijn minst bevreemdend dat in de hedendaagse verloskunde, waar het streven gericht is op een optimalisering van het baringsgebeuren, dit fenomeen zonder enig voorbehoud lijkt te worden geaccepteerd.

XIII

Het afsluiten van een verloskundig dossier zes weken postpartum staat een juiste evaluatie van de kwaliteit van het verloskundig handelen in de weg.

XIV

De aard der voorgenomen uitbreiding van het takenpakket van de vroedvrouw vormt eerder een argument ter faveure van de handhaving van deze fraaie oorspronkelijke beroepsaanduiding, dan dat het de naamsverandering in "verloskundige" rechtvaardigt.

XV

Er zijn te veel pillen.

XVI

De belangrijkste bijdrage tot een succesvolle therapie van de septisch-toxische shock wordt geleverd door een vroegtijdige herkenning van dit vaak levensbedreigende ziektebeeld. Een attente verpleegkundige staf is in deze van onschatbare waarde.

XVII

a. De klassieke talen ontbreken in de "pakketten" van vele middelbare scholieren met aspiraties tot het volgen van een medische studie.
b. Een waardevol onderscheid, zoals dat bijvoorbeeld gemaakt kan worden door het opnemen van één van beide prefices "dis-" of "dys-" in een compositum, dreigt ten onder te gaan in een grauwe poel van medische taalverarming.

XVIII

De bijzondere positie welke het schaap inneemt binnen het kader van de perinatologie ligt reeds van oudsher besloten in het Nederlandse volkswijsje:

IXX

Een wiskundeknobbel vormt tegenwoordig zelden een obstetrisch bezwaar.